

Emotion Processing in Autism Spectrum Disorder

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Declaration

My contribution to the work presented in this thesis spans each element of the study, from task design, data collection and analysis. However in such a multidisciplinary field as brain imaging in psychiatry, contributions have been made by a variety of colleagues as outlined below.

I recruited all study participants to the study however the recruitment of ASD participants was facilitated by the staff at Number 6. This process began in November 2006 and behavioural testing took place from then until May 2007. Several tasks included in the behavioural study (chapter 3) were tasks contributed by other researchers. The Ekman60 and Ekman Hexagon were provided by Dr Reiner Sprengelmeyer. The Emotional Body Movement task was provided by Dr Anthony Atkinson and Dr Winand Dittrich. The Emotional Voice task was provided by Dr Andrew Calder. The Social Cognition task was provided by Professor Andy Young and Dr Isabel Santos. I was solely responsible for the collection of behavioural data and completion of the diagnostic assessment.

Within the imaging study, the basic fMRI task was originally developed by Dr Jeremy Hall. The tasks presented in this thesis were adapted from this, involving the inclusion of stimuli provided by Dr Anthony Atkinson. Scanning took place at the SHEFC Brain Imaging Centre, Western General Hospital, where the radiographers were responsible for data acquisition. I carried out all pre-scan preparation and accompanied study participants to and from the scanner. During data collection I operated the experimental functional imaging equipment (the IFIS system). Scanning took place between October 2007 and April 2008.

Analysis of the imaging data was carried out in line with pre-existing protocols developed in the Division of Psychiatry and with the assistance of Liana Romaniuk, Elvina Gountouna and Dr Heather Whalley.

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This work has not been submitted for any other degree or professional qualification. I declare that this thesis is my own work, and the contribution to this thesis of others is clearly documented here and throughout the thesis where relevant.

Signed _____

Date _____

Publications

The paper cited below is currently in press at Psychological Medicine. Results presented in chapter 3 overlap with data included in this manuscript. A copy is included in the appendix.

Ruth C. M. Philip, H. C. Whalley, A. C. Stanfield, R. Sprengelmeyer, I. Santos, A. W. Young, A. P. Atkinson, W. H. Dittrich, A. Calder, E. C. Johnstone, S. M. Lawrie, J. Hall. *Deficits in facial, body movement and vocal emotional processing in autistic spectrum disorder*. Submitted.

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Abstract to be presented at the 8th Annual International Meeting For Autism Research, Chicago, 2009. Data included in chapter 4.

Ruth C. M. Philip, Andrew C. Stanfield, Jeremy Hall, Heather Whalley, Stephen M. Lawrie. *Lack of emotion modulation of brain activation during face processing in ASD*.

Abstract

With an estimated prevalence of ~1%, Autism Spectrum Disorder (ASD) is relatively common. Whilst accepted as a neurodevelopmental disorder, currently the diagnosis of autism is based on the observation of characteristic behaviour: deficits in language, communication and social skills in addition to unusual or restricted interests. Research in the condition has been approached with psychological and physiological methodology however a full understanding of the underlying neuropathology of autism is still unclear. Functional Magnetic Resonance Imaging (fMRI) has been employed to study face processing in ASD with varied results. The processing of other types of social cues has been far less extensively explored and similarly, whilst there have been some reports of aberrant neural responsiveness to emotion in ASD, this component of social cognition requires further study. In particular, it is unclear whether there is a specific deficit in processing faces in ASD or rather a global deficit in emotion processing which is present across stimulus types, sensory domains and emotions.

In this study basic emotion labelling using a range of stimulus types has been investigated within the same ASD cohort. In comparison to a control group, deficits were apparent in the ASD group when processing emotion in face, whole body and voice stimuli. This indicates a global emotion processing deficit in ASD that cannot be fully accounted for by deficits in basic face processing alone. Processing neutral and emotional faces and static whole body images was subsequently investigated using fMRI. When neutral faces, neutral bodies, fearful faces and fearful bodies were contrasted with fixation baseline, both groups broadly recruited the expected network of brain regions. When the emotional condition was contrasted with the neutral condition for each stimulus type significant between groups differences were apparent. The bilateral inferior parietal lobe responded significantly differently in response to facial emotion and the right supplementary motor area and superior temporal sulcus region was differentially activated in response to emotion in body stimuli.

Findings reported here suggest that there are wide ranging social deficits in ASD which relate to the processing of a variety of social cues. fMRI evidence suggests that these deficits have a neural basis, in which elements of the social brain, including regions associated with mirror neuron function, activate in an atypical manner in ASD.

Chapter 1 - An Introduction to Autistic Spectrum Disorder

1.1 Introduction

Autism is the term used to describe an individual with difficulties in three behavioural domains that become apparent in early childhood. These domains are: 1) language and communication, 2) social interaction and 3) the range and nature of interests and activities (American Psychiatric Association, 2000). These individuals, as well as arguably less severe cases in which not all of these criteria are met, are thought of as lying on the autism spectrum and thus described as having an Autism Spectrum Disorder.

The most recent UK-based autism prevalence study indicated that around one percent of the child population has an Autism Spectrum Disorder (Baird et al., 2006). This equates to approximately 700 children in Edinburgh alone, exerting an enormous pressure on health, education and social services as they attempt to meet the specific needs of children with this complex disorder. As a life-long condition it is reasonable to predict similar prevalence rates in the adult population and therefore a similar impact on adult services. With one in every hundred people experiencing some kind of difficulty in communication and social interaction, it is clear that autism has a substantial impact on society.

1.2 Historical background of autism

It has been suggested that as far back as the 17th century, within the fairytale of Sleeping Beauty, the alive yet isolated and untouchable state that the princess falls into could be an analogy of autism (Frith, 2003). Arguably there are various descriptions dating back hundreds of years which are consistent with the modern day conceptualisation of autism, for example the Wild Boy of Aveyron and the case of Hugh Blair discussed below (Frith, 2003).

At the end of the 18th century in France, The Wild Boy of Aveyron (Victor) was discovered; a 12 year old boy who it appeared had been living in the wild. He was initially described as having “constitutional imbecility” and appeared to be totally asocial, displaying dysfunctional behaviour in all three domains characteristic of autism. In addition to having no verbal language, non-verbal aspects of communication were impaired; abnormal gaze, vocalisations and gait were all noted. Reciprocal social

interactions were grossly impaired; following several years of specialised education, Victor failed to develop a sense of gratitude towards his caregivers, not even acknowledging the person feeding him. Victor was described as being “indifferent to childish amusements” and engaged in atypical and repetitive activities such as running straw through his teeth and rocking. Further to this, whilst generally considered to be an imbecile Victor could carry out some complex tasks with ease, such as making himself a meal. From reviewing the descriptions recorded it would seem that Victor meets criteria for what today would be called autism, however the severe social isolation he experienced during his childhood may provide some account for his autistic behaviour.

The case of Hugh Blair also provides another example of an individual with autism who predates the introduction of the term by many years. Detailed court records in Edinburgh describe behavioural features consistent with autism, without the influence of environmental insults such as the severe isolation suffered by Victor. In this case Hugh Blair was well tolerated due to his high societal standing but deemed mentally incapable and was generally thought of as deaf due to his inability to respond appropriately to speech.

The term ‘autism’ was not in fact introduced until 1910 when Eugen Bleuler used it to describe symptoms of schizophrenia. Bleuler derived the word from the greek ‘autos’ meaning ‘self’ and used it to describe “withdrawal of the patient to his fantasies, against which any influence from outside becomes an intolerable disturbance” (Kuhn and Cahn, 2004).

The first use of ‘autism’ to describe a childhood syndrome of social dysfunction was in a report published in the United States by Kanner in 1943. The manuscript included detailed case reports on 11 individuals displaying a constellation of impairments, key among which were “inborn autistic disturbances of affective contact” (Kanner, 1943). Whilst each individual differed in the degree and specific details of their impairments, common characteristic emerged. Kanner described them as having delays or absence of language development and often the presence of echolalia (the repetition of another’s

speech). In terms of their social skills Kanner commented that their “relation to people is altogether different” and that whilst they demonstrated an “inability to relate themselves to others” they formed “good relation(s) to objects”. The term “extreme autistic aloneness” was also coined in this report to describe the isolated nature of these individuals. In addition to these deficits in social behaviour Kanner noted that the children were “monotonously repetitious”, showed an “anxiously obsessive desire for the maintenance of sameness” and a limited “variety of spontaneous activity”. Further commonalities were also noted: excellent rote memory skills, sensitivity to loud noises and moving objects, the suggestion of good cognitive potential and finally all 11 cases came from highly intelligent families. Whilst psychotic disorders in children had been recognised for the previous fifty years, it was Kanner’s report that prompted the differentiation of children with autism from those generally labelled with childhood schizophrenia.

In 1944, Hans Asperger independently described a set of individuals with common social impairments and described them as having ‘autistic psychopathy’ (Asperger, 1944). The term Asperger Syndrome has since been adopted to describe these individuals. Asperger’s report focused more on the impairment of two-way social interaction. Whilst abnormalities in language were commented on, the development of language was not delayed in this cohort and they were more cognitively able than those described by Kanner. The report was originally published in German and only in the 1970s was the term Asperger Syndrome established to describe individuals fitting this profile of autism.

Since autism was recognised as a disorder distinct from childhood schizophrenia and general intellectual impairment various theories have been offered to explain the origins and nature of autism. In his original report Kanner comments on a potential marker of abnormal neurodevelopment in his cohort stating that five of his eleven subjects had relatively large heads (Kanner, 1943). However later in the 1960’s Kanner showed support for the psychodynamic theories that were put forward, influenced by the zeitgeist that existed in American psychiatry at that time. Possibly most famous was Bettelheim’s theory which ascribed the development of autism to ‘refrigerator mothers’ whose cold

mothering style prevented their children from developing typical relationships and social skills (Bettelheim, 1967). This idea has long since been disregarded. However there have been recent reports of mild autistic symptoms [described as the broader autism phenotype (Dawson *et al.*, 2007, Dawson *et al.*, 2002)] in the parents of autistic probands. It may have been that these subtle and sub-clinical levels of social and communication impairments present in some of the mothers of children with autism formed the basis of this theory.

Despite the difficulty in identifying the underlying aetiology responsible for autism, based on behaviourally observable characteristics autism was first recognised as a diagnostic category in DSM-III in 1978. These diagnostic criteria have since undergone several revisions, especially following Wing and Goulds epidemiological study where a larger cohort of individuals were assessed than those initially reported on by Kanner and Asperger (Wing and Gould, 1979).

1.3 Clinical definition of autism

Today autism is thought of as a condition with a broad clinical phenotype encompassing a wide range of behaviour and degree of global intellectual impairment. This widely diverse clinical population is generally described as having an Autism Spectrum Disorder (ASD). Individuals matching the description provided by Kanner are generally referred to as having classic or infantile autism whereas individuals demonstrating social impairments but without a delay in language development or cognitive ability receive a diagnosis of Asperger Syndrome. However both are considered to be an Autism Spectrum Disorder. The diagnosis of Pervasive Developmental Disorder – not otherwise specified (PDD-nos) is also included within the autism spectrum and is similar to the concept of atypical autism. This term is used to describe individuals who show a severe and pervasive impairment in the development of reciprocal social interaction that may be associated with language impairment or with the presence of stereotyped behavior. However due to atypical or subthreshold symptomatology or a later than usual age of onset, these individuals do not meet criteria for a diagnosis of autism.

Autistic Spectrum Disorders are defined and diagnosed by the observation of characteristic behaviour in three areas originally identified by Kanner and Asperger: impairments in language, impairment in social interaction, and the presence of a restricted and repetitive range of interests and behaviours. These features are outlined in more detail in relation to diagnostic criteria (DSM-IV) in tables 1.1 and 1.2 (American Psychiatric Association, 2000).

1.3.1 Impairments in language

Firstly, individuals with ASD demonstrate deficits in their expressive language, manifested by qualitative impairments in communication. This could range from a delay in the acquisition of spoken language to, in more severe cases, a complete lack of language development. However, even when language develops there can be an inability to initiate and sustain conversation as well as other, often subtle, abnormalities in speech. The selection of idiosyncratic vocabulary and the repetition of particular phrases are examples of speech abnormalities specified in DSM-IV criteria. However, echoing another's speech (echolalia) and limited or exaggerated variation in the tone or volume of speech are also often observed as are deficits in the meshing of verbal speech with nonverbal communication such as eye gaze and gesture. The diagnosis of Asperger Syndrome requires that there has been no clinically significant general delay in language acquisition, however in practice the more subtle abnormalities of speech described above are often present.

1.3.2 Impairments in social interaction

Secondly, social interaction and the understanding of others language and intentions are also disrupted in ASD. The same features are used to assess this in the diagnosis of both autism and Asperger Syndrome. These include deficits in non-verbal aspects of communication; lacking eye-contact, facial expression and gesture, as well as a failure to spontaneously initiate the sharing of interests with others. Social impairments may manifest as a lack of social reciprocity and insight into their own and others emotions. Finally, individuals with ASD often fail to develop typical relationships with peers and family.

1.3.3 Restricted and repetitive behaviour

The third behavioural characteristic required to make a diagnosis of ASD is the presence of restricted, repetitive and/or stereotyped interests or behaviours. The observable behaviour required to meet this criteria are variable and can be an abnormally intense interest or a preoccupation with a particular detail or element of something. It may also be that there is an adherence to a routine to a degree that is neither functional nor flexible. In more severely affected individuals motor mannerisms may be observed that are repetitive and stereotyped in nature, often referred to as self-stimulatory behaviours.

Finally, a range of intellectual impairment has also been reported in individuals with Autism Spectrum Disorders. Whilst it is stated in DSM-IV criteria for Asperger Syndrome that there is to be no significant cognitive developmental delay, individuals diagnosed with autism are generally subdivided into high and low functioning based on the Intelligence Quotient (IQ) cut-offs for learning disability (<70).

1.4 Autism as a neurodevelopmental disorder

Whilst clinically defined by observable behaviour, autism is broadly accepted as a neurodevelopmental condition and is investigated in terms of the physiology that may underlie the autistic behaviour.

1.4.1 Genetics

As mentioned earlier, there is growing evidence for a 'broader phenotype' of autism, used to describe relatives of autistic probands who display a higher level of autistic traits than found in the general population. When comparing the younger siblings of children with autism to controls, impairments have been reported in a variety of social and communicative skills including directing attention, understanding words and phrases, the use of gesture and social-communicative interactions with parents (Stone et al., 2007). Further evidence of this broader autism phenotype comes from studies of parents, where autistic traits such as impaired emotion processing (Szatmari et al., 2008) and language skills (Ruser et al., 2007) have been reported.

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DSM-IV diagnostic criteria for autism

A) A total of six (or more) items from 1, 2, and 3 with at least two from 1, and one each from 2 and 3:	1) qualitative impairment in social interaction, as manifested by at least two of the following:	<ul style="list-style-type: none"> a) marked impairment in the use of multiple nonverbal behaviours, such as eye-to- eye gaze, facial expression, body postures, and gestures to regulate social interaction b) failure to develop peer relationships appropriate to developmental level c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest) d) lack of social or emotional reciprocity
	2) qualitative impairments in communication, as manifested by at least one of the following:	<ul style="list-style-type: none"> a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime) b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others c) stereotyped and repetitive use of language or idiosyncratic language d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
	3) restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities as manifested by at least one of the following:	<ul style="list-style-type: none"> a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus b) apparently inflexible adherence to specific, non-functional routines or rituals c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting or complex whole-body movements) d) persistent preoccupation with parts of objects
B) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: social interaction; language as used in social communication; or symbolic or imaginative play.		
C) The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.		

Table 1.1 – the current DSM-IV criteria used for the diagnosis of autism (AmericanPsychiatricAssociation, 2000).

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DSM IV criteria for Asperger disorder

- | | | |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A) | Qualitative impairment in social interaction, as manifested by at least two of the following: | <ul style="list-style-type: none"> 1) marked impairment in the use of multiple nonverbal behaviours, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction 2) failure to develop peer relationships appropriate to developmental level 3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people) 4) lack of social or emotional reciprocity |
| B) | Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following: | <ul style="list-style-type: none"> 1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus 2) apparently inflexible adherence to specific, non-functional routines or rituals 3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements) 4) persistent preoccupation with parts of objects |
- C)** The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.
- D)** There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).
- E)** There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.
- F)** Criteria are not met for another specific pervasive developmental disorder or schizophrenia.

Table 1.2 – the current DSM-IV criteria used for the diagnosis of Asperger’s syndrome (AmericanPsychiatricAssociation, 2000).

In order to quantify this further, the Broader Phenotype Autism Symptom Scale has been developed, designed to measure social motivation, social expressiveness, conversational skills, and flexibility (Dawson et al., 2007). The Broader Autism Phenotype suggests familial links influence the presence of autistic behaviour however shared environmental factors may also account for this. More convincing evidence for a genetic basis of autism comes from sibling and twin studies.

There is a 2-8% chance that the sibling of a child with autism will also be affected by the condition, which is greater than the risk found in the general population [reviewed by Muhle et al (2004)]. In a twin study of autism, no same sex dizygotic twins were concordant for autism diagnosis whereas monozygotic twins had a concordance rate of 60% (Bailey *et al.*, 1995, Muhle *et al.*, 2004). Whilst a monozygotic concordance rate of 100% would be required to conclude that autism has a purely genetic basis, the increased rate of concordance with increased levels of genetic homogeneity displayed in sibling and twin studies suggests that there is a genetic influence on the development of autism.

Whilst there was no concordance for the diagnosis of autism in same sex dizygotic twins in this sample, ~10% displayed some kind of social or cognitive delay. In monozygotic twins this figure was reported to be 92% (Bailey et al., 1995). These figures support the notion that a broader autism phenotype exists, mediated by genotype.

Whilst this evidence suggests that the genetic picture of autism is far from simple and likely has a multi-locus genetic basis, it adds further weight to the conceptualisation of autism as a neurodevelopmental disorder requiring physiological investigation.

1.4.2 Brain structure

Early evidence for abnormal neuroanatomy in autism was alluded to by Kanner who commented that five of his eleven subjects had relatively large heads (Kanner, 1943). Subsequent studies measuring the head circumference of autistic children have suggested accelerated brain growth as a neuropathological feature of autism (Courchesne et al., 2003). There have been a limited number of post-mortem studies in which stereological

methods have been applied to investigate the neuronal organisation of the brain in autism. These have reported increased cerebral neuron density, decreased density of Purkinje cells in the cerebellum and poorly defined laminar patterns although this was not consistently found in each autistic brain studied [reviewed by Amaral et al (2008)].

The application of MRI to investigate the neuroanatomy of autism has led to many (often contradictory) reports of volumetric differences in brain regions in groups of individuals with autism in comparison to controls. The heterogeneous make up of the population diagnosed with Autism Spectrum Disorder in addition to the small sample sizes studied likely accounts for these contradictions. Co-morbidity with epilepsy and learning difficulties will confound findings as could the influence of medication. Most importantly, as a neurodevelopmental condition the chronological age and stage of development of the study participants will also impact on brain structure findings. Following a meta-analysis of this body of literature taking into account the effects of age and IQ, Stanfield et al (2008) report that total brain volume, including cerebral hemispheres and cerebellar volume, is increased in ASD, as was caudate nucleus volume. Corpus callosum area was found to be reduced in ASD.

1.4.3 Functional neuroanatomy

There have been a variety of reports describing patients with acquired brain damage who have developed social impairments and other characteristics of autism; patients with traumatic brain injuries demonstrate lower levels of empathy (Wood and Williams, 2008) and deficits in maintaining relationships (Engberg and Teasdale, 2004). Whilst none of the cases in these studies were recognisably autistic this is not surprising given that autism is known to be present from very early childhood (and possible even *in utero*) hence insults to a more mature brain would be expected to manifest rather differently. What these studies provide is evidence that malfunction of specific brain regions can result in behavioural symptoms similar to those seen in autism, again providing further evidence that there is a neural substrate underlying autistic behaviour.

Functional imaging provides a methodology to study the functional organisation of the brain in people with autism. Positron Emission Topography (PET), Single Photon Emission Computer Topography (SPECT) and functional Magnetic Resonance Imaging (fMRI) have all been applied to autistic cohorts. Both PET and SPECT studies have provided evidence for differences in cerebral blood flow and glucose metabolism in individuals with autism (Ohnishi *et al.*, 2000, Zilbovicius *et al.*, 2000). Findings from the fMRI literature will be reviewed in detail in chapter 2. In summary, there appears to be convergent evidence for neurophysiological abnormalities in autism.

Current physiological investigation of ASD has underlined that autism is a condition underpinned by dysfunctional neural development; the exact nature of the physiological substrate is still unclear. As a condition with specific deficits in such complex cognitive skills as language and social interaction, the neurophysiological investigation of autism must be carried out in conjunction with psychological approaches.

1.5 Psychological theories of autism

Several psychological theories have been proposed to try to account for such a broad ranging behavioural phenotype, to unite the diverse population with autism and to elucidate the core cognitive feature responsible for the profile of autistic impairments. The three theories which have received the most attention are Executive Dysfunction Theory, Weak Central Coherence and Theory of Mind (Happé and Frith, 1996, Rajendran and Mitchell, 2007). Each offers an account of autism based on cognitive psychology, attempting to link brain function with observable autistic behaviour.

1.5.1 Executive Dysfunction Theory

Repetitive behaviours and strict adherence to routines are features of autism shared with some patients with acquired frontal lobe damage. These patients also demonstrate deficits in executive function which is unsurprising given the evidence for the involvement of the prefrontal cortex in accomplishing such tasks (Tanji and Hoshi, 2008). Executive function encompasses a variety of components involving planning and organisation, response monitoring, attention shifting; in short the management of several

cognitive processes. The elements of executive function proposed to be aberrant in ASD mainly relate to planning, mental flexibility and response inhibition (Hill, 2004) and evidence for this is discussed below.

Deficits relative to control groups have been identified in ASD cohorts when participants have been asked to complete the Tower of London task (Hughes et al., 1994). This task (illustrated in figure 1.1a) requires participants to plan several strategic moves in order to successfully complete the puzzle. Deficits in this task, whilst considered to represent an executive dysfunction, may also be influenced by a weak central coherence processing style (discussed in full later) with which individuals struggle to consider each individual move as part of an overall solution to the puzzle.

Mental flexibility has been investigated in ASD using the Wisconsin Card Sorting Test (figure 1.1b) in which participants must switch between rules in order to continue to respond correctly to trials (Kaland et al., 2008). The ASD group was reported to be poorer than controls in switching to new rules during the task. Dysfunction in this area may account for the difficulty many individuals with autism have in regulating and modulating their behaviour and may explain the tendency people with ASD can have to engage in repetitive activities.

There is also evidence to suggest that there is a deficit in ASD in relation to response inhibition which again may account for the presence of repetitive behaviours and the preference for sameness that many individuals with ASD display. This inhibition dysfunction appears to be apparent primarily in tasks in which a proponent response requires inhibition (Ozonoff et al., 1994).

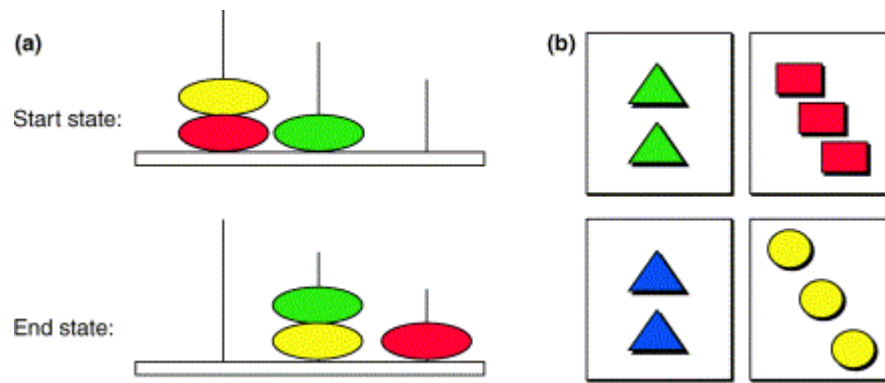


Figure 1.1 – Schematic of a) the Tower of London task, an executive function task aimed to assess planning skills and b) stimuli from the Wisconsin Card Sorting Task which is used to investigate set shifting (Hill, 2004).

Whilst executive dysfunction theory acknowledges the cognitive deficits and motor behaviour characteristic of autism, it is less clear how it can account for the specific language and social impairments. Further to this, in a population where the majority have a co-morbid global intellectual impairment it is not surprising that deficits manifest in cognitive tasks of executive function. The theory lacks uniqueness to autism as other clinical populations demonstrate deficits in executive function e.g. schizophrenia (Kerns et al., 2008) and attention deficit hyperactivity disorder (ADHD) (Doyle, 2006). However, the impairments seen in tasks of executive function in ASD may provide an example of a more general impairment in the integration of brain regions into a network to accomplish a function. When regarded in this way, it is possible to hypothesise that this integration dysfunction could also account for the other deficits seen in autism in language and social skills - cognitive capabilities that require the successful recruitment and integration of dispersed brain regions to achieve.

1.5.2 Weak Central Coherence

Evidence that those with ASD showed enhanced ability in tasks requiring detailed-focussed processing was emerging in the late 1980s and following on from this Happé and Frith proposed the theory of Weak Central Coherence as an explanation for several behavioural characteristics of autism (Frith and Happé, 1994). The idea proposed is that individuals with ASD have a tendency to perceive component parts rather than the whole gestalt reducing their ability to integrate context and understand 'the bigger picture'. It is

possible to see how weak central coherence could relate to difficulties in language and social understanding which require interpretation of context and the integration of signals from a variety of sources to accomplish. It also is possible to relate this theory to the preference many individuals with autism show for detail and particular features of objects. Increased attention to detail could also explain the apparent oversensitivity to change in elements of a routine observed in ASD, details which are generally thought of as insignificant to typically developed individuals. Whilst applied above to explain negative characteristics of ASD the Weak Central Coherence theory is the only theory which proposes a different cognitive style as an explanation for autistic behaviour rather than simply a dysfunction. A focus on detail could account for the enhanced 'savant' abilities often observed in individuals with autism e.g. having perfect pitch and creating incredibly accurate drawings from memory.

This feature of the theory has been exemplified in several studies in which both enhanced and poorer performance in the ASD group has been observed and accounted for by a cognitive style characterised by weak central coherence. ASD performance on tasks requiring processing of component parts has been reported to be greater than that of control groups supporting a local processing bias (Happé and Frith, 2006). The Embedded Figures Task (illustrated in figure 1.2) in which participants are required to find a simple shape embedded within a more complex design is an example of an activity in which those with ASD tend to show enhanced performance (Jolliffe and Baron-Cohen, 1997, Shah and Frith, 1983). However in tasks requiring attention to context, like the pronunciation of homographs e.g. read, wind, live, ASD group performance has been reported to be impaired (López and Leekam, 2003).

This theory has also been proposed to support early reports of a lack of configural processing of faces in autism. Whilst control groups show a decrease in task performance when face stimuli are presented inverted (and therefore no longer in their usual configuration,) this dip in performance is not seen in individuals with autism, hypothesised to be due to their piecemeal approach to face processing (Langdell, 1978).

More recent applications of the face inversion task have provided evidence of intact configural face processing in ASD (Lahaie *et al.*, 2006, Teunisse and de Gelder, 2003).

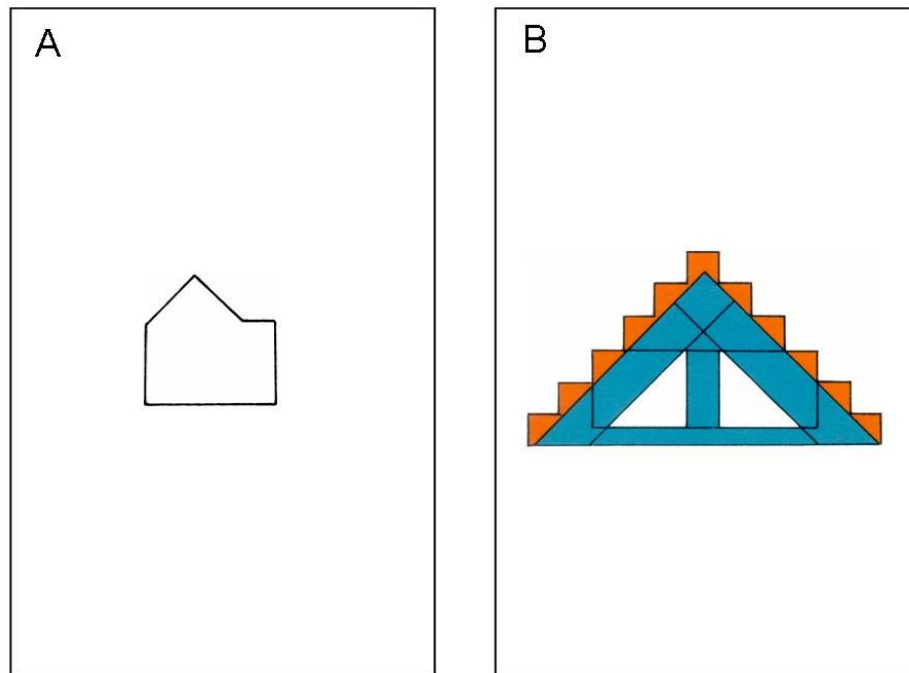


Figure 1.2 – An example of the stimuli used in the Embedded Figures Task. Participants are asked to find the simple shape (A) within the complex shape (B).

Indeed evidence exists to suggest that individuals with ASD can in fact successfully complete tasks requiring strong central coherence. This suggests that whilst there may be a predisposition in ASD to attend to details, the ability to process more general information is still present or that at least weak central coherence is not a universal feature of autism (Mottron *et al.*, 2003, Mottron *et al.*, 1999). Furthermore, given the severely disabling features which many people with autism have it is hard to see how a disposition towards a cognitive style could provide a complete account for autistic behaviour.

1.5.3 Theories of social impairment

Originally proposed by Baron-Cohen and colleagues (1985) the most widely known social impairment theory proposed to account for the autistic phenotype suggests impaired development of a Theory of Mind; or rather that people with autism have a deficit in ‘mentalizing’ i.e. attributing mental states and intentions to others. Deficits in Theory of Mind (ToM) processing could account for the social difficulties presented in ASD, and as remarked by Hill and Frith (2003) deficits in mentalizing can provide a potential explanation for the seemingly contradictory manifestation of social dysfunction in ASD where individuals can appear to be aloof and disinterested in social contact or have an indiscriminate social approach.

The first task designed to measure an individual’s ability to attribute a false belief to another was carried out by Wimmer and Perner (1983). This task was adapted slightly by Baron Cohen et al (1985) and now the Sally-Anne task is the most famous means by which to assess Theory of Mind ability. This task is outlined in figure 1.3. Typically developing children pass this test by the age of four whereas 80% of the mental age matched autistic children tested failed this false belief test. The children with autism tended to respond in line with their own knowledge of events failing to take into account the knowledge and subsequent beliefs held by the characters in the story. This phenomenon has also been observed in adults in other tasks involving mental state attribution such as those that require non-literal interpretation of language directed by social context e.g. understanding irony (Martin and McDonald, 2004).

Whilst there have been repeated findings that mentalizing is a skill that is deficient in ASD, it is unclear whether ToM deficits are a universal feature of autism; 15 – 55 % of experimental groups with autism pass first order false belief tests (Happé and Frith, 1996). A key element of this theory that is sometimes overlooked however is that mentalizing is an intuitive skill in typically developed individuals. So whilst some people with ASD have learnt to consider the perspectives of others or apply logic to reason out the intentions behind another’s actions, their impairment lies in their inability to do this intuitively. This acquired and conscious ToM skill may be effective in specific

laboratory-based ToM tasks, but may be insufficient to facilitate the constitutive mentalizing requirements of day to day communication.

Another concern when considering the universality of Theory of Mind deficits in ASD is that due to the co-morbid intellectual impairment and limited language skills seen in many individuals with ASD, a large percentage of the autistic population cannot complete standard assessments of mentalizing ability. It is also unclear how deficits in Theory of Mind can account for the restricted interests/motor stereotypies or the profile of cognitive abilities seen in autism. Further to this, it is also unclear whether a deficit in mentalizing is a deficit specific to autism; groups of learning disabled children, adults with schizophrenia and people with psychotic and non-psychotic depression have all demonstrated deficits in theory of mind tasks equivalent to those seen in autism (Brune, 2005, Happé and Frith, 1996, Wang *et al.*, 2008).

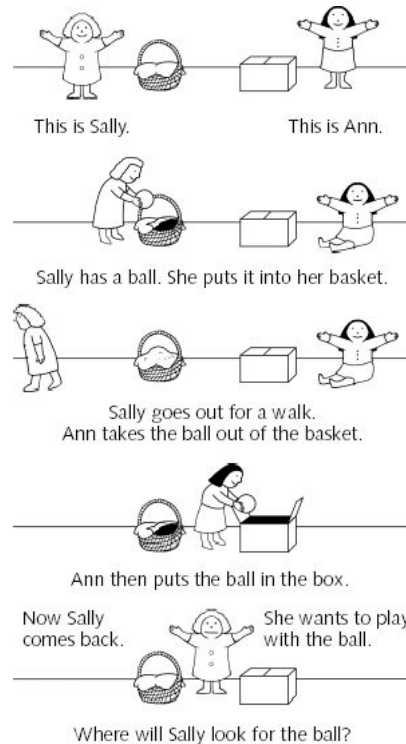


Figure 1.3 – A cartoon explaining the scenario acted out during the Sally-Anne task, used to assess theory of mind.

Whilst deficits in Theory of Mind are perhaps the most broadly researched social impairment theory in autism, deficits in interpersonal relatedness (Walters et al., 1990), joint attention (Bruinsma et al., 2004) and imitation (Williams et al., 2001) have also received attention and would seem more relevant to the investigation of autism as a developmental disorder. In typically developing children the ability to attribute mental states to others does not develop until the age of four, whereas autism is often already diagnosed by this stage and retrospectively developmental deficits are frequently present from even earlier. So whilst the study of imitation and joint attention has received somewhat less attention in the literature, it would seem more likely that these more primitive elements of social development are responsible for later social deficits such as impairments in mentalizing. Similarly, the investigation of more basic elements of social communication e.g. emotion recognition, is also an area of great interest in the study of ASD.

1.5.4 Emotion processing

1.5.4.1 Face emotion processing

Some of the earliest evidence for aberrant emotion processing in autism came from a study by Weeks et al (1987) of facial processing. In contrast to a control group, children with ASD tended to sort pictures of faces on the basis of non-emotional features, suggesting insensitivity to the emotional facial expressions of others. Studies have since identified deficits in emotion recognition in both children (Celani et al., 1999) and adults with ASD (Adolphs *et al.*, 2001, Hobson *et al.*, 1988b, Howard *et al.*, 2000, Pelphrey *et al.*, 2002). Two studies, by Pelphrey et al (2002) and Howard et al (2000) identified a differentially severe deficit in the identification of face stimuli expressing fear.

There is also evidence to suggest that understanding more complex emotional and socially relevant information from facial stimuli is impaired in autism. In a revised version of the “Reading the Mind in the Eyes” test, Baron-Cohen et al (2001a) found that adults with Asperger Syndrome (AS) or High Functioning Autism (HFA) were markedly impaired in assigning the correct complex mental state (e.g. reflective) to images of eyes compared to controls. Adolphs et al (2001) reported abnormalities in HFA participants at

making social judgements of trustworthiness and approachability from facial stimuli. Interestingly, making social judgements from lexical stimuli was preserved in the autism group in this study, suggesting that their deficit might lie in the processing of emotional face stimuli specifically.

1.5.4.2 Processing emotion from body movement

There is some evidence to suggest that the abnormalities of emotion processing observed in autism may be a general impairment that crosses modalities or types of stimuli. Moore et al (1997) asked participants to describe point-light movies of people and found that autistic individuals performed as well as controls in describing simple actions but showed a trend towards impairment when labelling emotional and subjective states. Hubert et al (2007) have since shown that an autistic group were specifically impaired in describing a range of emotional and subjective states from biological motion stimuli. However there is also evidence to suggest that the ability to process biological motion regardless of emotional content is impaired in autism. In comparison to mental age matched controls, autistic children were found to be significantly impaired in discriminating point-light displays of everyday actions (e.g. running, kicking, throwing) from phase scrambled versions of the same displays (Blake et al., 2003). In that study the deficit was found to be specific to biological motion as the performance of participants with autism was equivalent to the controls in tests of the perception of global coherent motion.

Cumulatively, this evidence suggests that individuals with autism may be impaired in recognising emotional content in a variety of stimuli. However, it has not been clearly established that the apparent deficits in emotion recognition in faces and from movement do not derive from impairments in other areas, such as the processing of visual stimuli.

1.5.4.3 Emotion in the auditory modality

Investigating emotion processing in the auditory modality is one way to tease these possibilities apart. If it is the case that the deficits in emotional processing of faces and whole body movement demonstrated in autism are a result of deficits in visual processing style and/or visual attention then emotional processing in the auditory domain would be

preserved. Findings from the limited literature on vocal emotion processing have provided mixed results. Hobson et al (1988a) found that a group of adolescents with autism and co-morbid learning disability performed less well than verbal ability matched controls when asked to match faces to emotional voices. This impairment was not evident in a similar task where participants were asked to match objects to sounds, with no emotional content. Conversely, Loveland et al (1997) found that emotion recognition of verbal and non-verbal stimuli expressing happiness, sadness, anger, surprise or neutrality was influenced by the level of ability in child, adolescent and adult subjects, regardless of autism diagnosis. It is important to note, however, that the tasks used in both of these studies involved vocal emotional stimuli in addition to emotion displayed in a different modality (faces or gestures) and therefore did not investigate vocal emotion processing in isolation. Rutherford et al (2002) carried out the Reading the Mind in the Voice task which involves stimuli purely in the auditory domain and demonstrated deficits in autistic participants' ability to extract complex mental states from dialogue. Simple recognition of basic emotional states from vocal stimuli was reported to be as accurate as controls in a group of adults with Asperger Syndrome in the recognition of happiness, sadness and anger (O'Connor, 2007). Mazefsky and Oswald (2007) investigated ability to label emotion in faces and voices in adults with ASD, divided into groups based on whether they had a diagnosis of High Functioning Autism or Asperger Syndrome. Whilst the Asperger Syndrome group performed equally well as the control group, the HFA group showed a significant impairment in both tasks. Therefore it remains unclear to what degree the recognition of emotion from voices is impaired in ASD.

In summary, there is behavioural evidence to suggest that there may be a global impairment of emotion processing in ASD. Studies thus far have however been biased towards investigating facial emotion and have employed a variety of methodologically diverse behavioural tasks to a range of child and adult ASD cohorts with mixed results. Consequently it remains unclear whether the reported deficits can in fact be accounted for by impairments of processing or attention in any one stimulus domain rather than a global emotion processing impairment. Answering this question will facilitate the search for the

neural substrate underlying the social deficits in ASD as well as potentially influencing the development of interventions. In addition, more clearly defining the nature of emotion processing difficulties will shape the understanding of the social impairments of ASD.

1.6 Conclusions

With an estimated prevalence of around 1%, Autism Spectrum Disorders clearly impact on society today. Although evidence exists to suggest that autism is not a modern day phenomenon, it is only within the last 60 years that autism has been regarded as a clinical condition and it is even more recently that autism has been accepted as a neurodevelopmental disorder. Due to the complexity of the behavioural phenotype a mix of cognitive psychology and neuropsychological approaches have been applied to the study of autism. From these, several well supported theories have been offered to explain the nature of autism, although none currently provides a full account of the range of behaviour encompassed in the autistic phenotype. Emotion processing has emerged as a relevant topic to investigate. In particular, whether or not individuals with ASD have a specific deficit in the processing of emotional information that supersedes differences in more basic visual processing deficits is a currently unresolved question which will be investigated in chapter 3. The advent of techniques such as fMRI also permits the investigation of the neural substrate of such a deficit. The current evidence from studies applying this technique to investigate ASD will be reviewed in chapter 2 and further fMRI investigation of emotion processing in ASD shall be presented in chapter 4.

Chapter 2 - A Systematic Review of the Investigation of ASD with Functional Magnetic Resonance Imaging

2.1 Introduction

Magnetic Resonance Imaging (MRI) is a relatively recent methodological development which allows images to be taken of the brain *in vivo* in a safe and non-invasive manner, without the need for ionising radiation. The first MRI pictures of a human were published in 1977 (Damadian et al., 1977) and since then the use of MRI to acquire images of internal anatomy, including the brain, has become commonplace. Further advancement of MR technology led to the development of functional MRI, which capitalises on the ferromagnetic properties of oxygenated and deoxygenated haemoglobin in blood cells to provide an indirect measure of brain activity. Thus fMRI provides a methodology for investigating the functional organisation of the brain. Whilst fMRI is today regarded as a well established technique used to research both typical and pathological brain function, appreciating the underlying neurophysiology of the technique is essential when interpreting fMRI data.

2.1.1 fMRI methodology

Blood Oxygen Level Dependent (BOLD) signal is the data collected during fMRI and is a signal which varies in relation to the level of deoxyhaemoglobin in the blood. As neurones become active their metabolic requirements increase which results in an alteration in the ratio of oxygenated and deoxygenated blood delivered to that region. Changes in the BOLD signal thus provide an indirect measure of the activity of neurones. Within fMRI experiments, different conditions are presented allowing for the brain activation between conditions to be contrasted.

There are two types of task design commonly used in fMRI experiments which relate to the way in which stimuli are presented. Each comes with its own merits and limitations. The first type is the block design where reasonably long blocks of each task condition are presented and several trials of the same condition type are presented within a block. The second type is an event related design where events of each condition type are interspersed.

Block designed tasks are generally regarded to provide greater statistical power during analysis compared to event related designs. In addition block design tasks can be simpler for the participant to complete successfully as there are fewer switches between conditions and task demands. The event related design is however, arguably more environmentally valid, it circumvents the issues of stimulus order predictability and minimises the likelihood of the habituation of the neural response to a particular stimulus type. Taking these factors into account, the optimum design for a given study ultimately depends on the specific question that the task is being designed to address.

BOLD signal changes in response to stimuli are characterised by the haemodynamic response function (HRF). In response to stimuli, there is an initial dip in oxygenation of blood hypothesised to be as a result of the initial energy requirements being met by local oxyhaemoglobin. This initial dip is not consistently reported, particularly in studies using a 1.5T scanner, where it is thought that the magnet strength is insufficient to detect this subtle change in BOLD signal. The more measurable aspect of the BOLD response occurs ~3 seconds after stimulus onset as oxygenated blood is supplied to the neurones requiring energy. This is sustained for several seconds before the concentration of blood oxygen returns to pre-stimulus levels, following a brief post stimulus undershoot. The temporal resolution of fMRI is therefore relatively slow and BOLD signal changes occur over a number of seconds, rather than the millisecond scale of neuronal activation.

2.1.2 Limitations of the method

As described above, the BOLD signal provides an indirect measure of brain activity. If a population of neurones requires additional oxygen, it can be assumed that they will be involved in processes requiring energy. However, at a cellular level there is a variety of processes that this could be, each with different energy requirements and acting over varying time scales. For example, the propagation of action potentials requires less energy for less time than the changes associated with more long term plasticity such as the up regulation of gene expression and protein production to allow insertion of increased numbers of postsynaptic receptors. So whilst changes in BOLD signal in a particular region indicate involvement in the prescribed task/stimuli processing, this is a

relatively crude measure which cannot provide sufficient detail to infer the kind of function that neuronal population may have in the process. Similarly, whilst the spatial resolution of fMRI allows us to isolate areas of activation to anatomically defined regions, this is still averaging the metabolic requirements of approximately 5.5 million neurons (Logothetis, 2008).

It is also important to consider that the involvement of both glutamatergic and GABAergic neuronal populations within a process will result in an increased BOLD signal, although the latter will be having an inhibitory influence. Furthermore, as mentioned previously, the relative nature of BOLD signal change can mean that the apparent failure of a hypothesised brain region to activate in an experimental condition may in fact indicate that the region is already active in the baseline condition i.e. there is no *differential* activation but that region is active during the experimental condition. Establishing the appropriate baseline condition for a task can be problematic. The majority of studies use a 'rest' condition, commonly involving participants viewing a fixation cross. However, having such an unconstrained non-task condition may not be ideal and generally studies will also include an additional baseline condition which matches the task condition as closely as possible, with the exception of the component of the task that is of particular interest.

Further issues in interpreting fMRI data relate to its acquisition and subsequent processing and analysis. Movement artefacts compromise the integrity of data and it is generally accepted that movement greater than approximately one voxel might necessitate exclusion from further analysis. Furthermore, the data acquired can be susceptible to differences in the integrity of surrounding tissue, for example signal loss is a common problem in regions bordering air sinuses e.g. frontal lobe.

Despite these methodological considerations, networks of brain regions have been repeatedly found to be activated in a range of tasks from basic visual processing to more complex cognitive paradigms. Also, the validity of fMRI to indicate brain activity has been supported by multimodal studies, employing additional metabolic and

electrophysiological imaging techniques (Krings et al., 2001). Functional MRI is a safe non-invasive way of collecting data which provides an indirect measure of brain activity in response to particular conditions, as defined by the experimental paradigm. As there is no use of radio-labelled tracers, fMRI can be used safely and even repeatedly, and as such lends itself well to the investigation of the differences in brain function which may underlie neurodevelopmental conditions such as ASD.

2.1.3 Application to ASD

Using fMRI in individuals with ASD presents a number of difficulties unique to this population. The MRI sequences required for data acquisition are very loud, and auditory hypersensitivity has been reported as a sensory issue in many people with ASD (Leekam et al., 2007). In addition, meeting new people and undergoing an unusual procedure outwith everyday routine may be particularly stressful for individuals with ASD who often feel anxious in new environments, particularly uncomfortable meeting new people, and can struggle with changes in routine. Further to this, participants are required to stay still to ensure the best quality of data acquisition. These challenges are not insurmountable, as evidenced by the growing literature of fMRI studies in ASD, but participants often require additional preparation and pre-training sessions.

The aim of this review is to 1) assess the ASD populations taking part in fMRI research in terms of how representative they are of the ASD population as a whole; 2) identify common findings across studies which indicate brain regions which function differently in ASD, relative to typically developed individuals.

2.2 Methods

2.2.1 Literature search methods

Medline, EMBASE and PsychINFO were searched for all English language studies published between January 1984 and August 2008 that reported functional MRI data in people with an Autism Spectrum Disorder. Search terms included ‘autism’, ‘Asperger Syndrome’, ‘pervasive developmental disorder’ and related terms were combined using the AND operator with ‘functional magnetic resonance imaging’ OR ‘fMRI’. Both free-

text and expanded medical subject headings were used. The search strategy was supplemented using a cited reference search and by inspecting the reference lists of included articles.

2.2.2 Inclusion criteria

Articles were included if they were primary research studies published as peer-reviewed articles in English and they compared a sample of participants with an Autism Spectrum Disorder with a group of healthy controls, using fMRI. Abstracts were assessed for inclusion, and full text articles were retrieved where appropriate.

2.2.3 Data extraction

For each study, demographic data for the ASD participant group were extracted; gender, mean age and mean IQ. Where possible, data pertaining to the diagnosis of the ASD group was also extracted, including the diagnostic criteria used. The selection of the comparison group and features by which they were matched to the ASD group was also recorded. Details of the fMRI paradigm were also extracted and studies grouped according to the element of cognition under investigation.

2.3 Results

2.3.1 Included papers

68 papers were identified reporting original research studies using fMRI to investigate ASD. Three of these were excluded as they concerned connectivity analysis of fMRI data published elsewhere (Mizuno *et al.*, 2006, Villalobos *et al.*, 2005, Welchew *et al.*, 2005). One article performed spectroscopy analysis in conjunction with fMRI data presented elsewhere and was therefore excluded (Kleinhans *et al.*, 2007). One article was excluded as it performed a pooled analysis from data sets published elsewhere (Cherkassky *et al.*, 2006). Three papers presented case studies so were also excluded (Carmody *et al.*, 2007, Grelotti *et al.*, 2005, Turkeltaub *et al.*, 2004). Finally, one study was excluded as it investigated a group of participants with autism pre and post treatment and did not investigate a comparison group (Bölte S, 2006). This left 59 original research papers in

which a group of participants with ASD were investigated using functional MRI paradigms, and compared to a control group.

2.3.2 ASD participant demographics

Seven studies failed to report the gender ratio in their sample. 57% of studies investigated only male participants. The ratio of males to females participating across all fMRI studies is 14:1. One study did not provide details of the age of the participants in their study (Just *et al.*, 2004). Of the remaining 58 studies, 15 investigated children and adolescents and 43 investigated adults. 95% of studies provided full scale IQ scores for the ASD participants in their study, predominantly measured using the WAIS or the WASI. Two studies did not assess full scale IQ but matched groups according to verbal IQ scores (Pinkham *et al.*, 2008, Thakkar *et al.*, 2008). Two studies provided no details of IQ measures (Belmonte and Yurgelun-Todd, 2003, Wang *et al.*, 2004). Of the remaining studies, the median FSIQ score was 105, with a reported range of 55 – 139. The majority of studies however only included participants with an IQ over 70.

From articles identified in this review, 662 participants with an Autism Spectrum Disorder were reported on. In 11 studies, participants were described as an unspecified combination of individuals with autism/high functioning autism and/or Asperger Syndrome and/or PDD-nos. In a further 4 studies, a total of 64 participants, were described as having an ASD, presumably encompassing the disorders mentioned above. The remainder of studies specified the diagnosis of participants; 364 had a diagnosis of autism (including ‘high-functioning autism’), 119 had a diagnosis of Asperger Syndrome and 9 had a diagnosis of PDD-nos. Expert clinical assessment was used for participant diagnosis which was generally supported by the use of DSM-IV criteria (in 32 studies) and ICD-10 criteria (a further 9 studies). The ADI and ADOS were commonly used as standardised diagnostic measures, in 49 and 41 studies respectively. However, according to some of the published scores, participants did not always meet the cut-off criteria on these instruments (Hadjikhani *et al.*, 2004a, Hadjikhani *et al.*, 2007) or scores for some participants were missing (Pierce *et al.*, 2001, Pinkham *et al.*, 2008). In studies with younger participants the Childhood Autism Rating Scale (CARS) assessment and the

Vineland Adaptive Behaviour Scale were applied [(Muller *et al.*, 2004, Muller *et al.*, 2003, Muller *et al.*, 2001, Pierce *et al.*, 2001) and (Schultz *et al.*, 2000) respectively]. The Autism Spectrum Quotient (AQ) and Social Responsiveness Scale were also used as measures of autistic symptoms [(Ashwin *et al.*, 2007a, Bird *et al.*, 2006) and (Wang *et al.*, 2006, 2007) respectively].

2.3.3 Summaries of fMRI findings

Details and summaries of each paper included in the review are in table 2.1.

2.3.3.1 Perceptual processing and executive function tasks

Basic visual perception in a group of adults with ASD was investigated using a visual checkerboard paradigm (Hadjikhani *et al.*, 2004b) and whilst results indicated that the basic organization of visual cortices is not disrupted in autism, several studies have gone on to investigate how this neural circuitry is engaged during visuo-spatial processing tasks.

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Allen (2003)	7:1	26.9 (8.6)	85 (11.95)	Autism	DSM-IV, ADI-R, ADOS	Age, gender, handedness, task performance	1) Self paced button press; 'rest' as baseline. 2) Button press to target; passive viewing of visual stimuli as baseline.	1) ASD > control; cerebellum. 2) Control > ASD; cerebellum. (ROI analysis)
Allen (2004)	7:1	26.9 (8.6)	85 (11.95)	Autism	DSM-IV, ADI-R, ADOS	Age, gender, handedness, task performance	Self paced button press; 'rest' as baseline.	ASD > control; ipsilateral anterior cerebellum. (ROI analysis)
Ashwin (2007a)	13:0	31.2 (9.1)	108.6 (17.1)	1 HFA, 12 AS	Clinical diagnosis, AQ	Age, IQ, gender, handedness, task performance	Button press in response to stimuli. Face condition (including high fear, low fear and neutral faces); scrambled face stimuli as baseline.	Control > ASD; left amygdala and orbitofrontal cortex. ASD > control; right anterior cingulate cortex and bilateral superior temporal cortex. <i>In the control group, intensity of fear modulated activity in bilateral amygdala, fusiform gyrus, right medial prefrontal cortex and superior temporal sulcus region, an effect not seen in the ASD group.</i>
Baron-Cohen (1999)	4:2	26.3 (2.1)	108.5 (10.5)	Autism, AS	DSM-IV, ICD-10	Age, IQ, handedness, socioeconomic status, education	Make a 2 alternate forced choice decision via button press on the mental state portrayed in eye stimuli; gender discrimination of same stimuli as baseline.	Control > ASD; left insula, inferior frontal gyrus and right insula. ASD > control; bilateral superior temporal gyrus.
Belmonte (2003)	5:1	32.7 (9.8)	'non-retarded'	Autism, AS, PDD-nos	DSM-IV, ADI	Gender, handedness, task performance	Attend to one location and switch attention when target stimuli observed; fixation baseline.	Control > ASD; bilateral superior parietal lobe and medial frontal gyrus, left medial temporal gyrus, postcentral gyrus and inferior frontal gyrus, right premotor cortex and medial frontal gyrus.
Bird (2006)	14:2	33.3 (11.5)	119 (14)	1 autism, 15 AS	DSM-IV, ADOS, AQ	Age, IQ, gender, task performance	1. Localiser task: passive viewing of neutral faces; passive viewing of houses; fixation baseline. (fixation cross over 'eye region') 2. Same/different discrimination in horizontal or vertical plane via button press; pairs of faces and houses presented.	1. No between group differences in any contrast. 2. Attend to houses vs not attend No between group differences. Attend to faces vs not attend Control > ASD group; left fusiform gyrus.

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Mean age (sd)	Autism group		Diagnostic measures	Control matching criteria	Task design	Main findings
			Mean IQ (sd)	Diagnosis				
Bolte (2008)	7:0	27.7 (7.8)	98 (19.2)	Autism	ICD-10, ADI-R, ADOS	Age, IQ, gender, handedness, task performance	1) Count triangles within Block Design stimuli; fixation baseline. 2) Counting colours; fixation baseline.	1) Control > ASD; right ventral quadrant of prestriate visual cortex (V2v) and ventral posterior visual cortex (VP). 2) Control > ASD; ventral posterior visual cortex (VP). (ROI analysis)
Chiu (2008)	12:0	16.5 (3.3)	103 (18)	Autism, AS, PDD-nos	DSM-IV, ADI, ADOS	Age, IQ, gender, task performance	Multiround trust game – investor (control subject) is given an amount of money and chooses to send a proportion of this to trustee (ASD subject). This is tripled and trustee then repays a proportion of the tripled amount. 1. 'other' condition; at the time of controls investment. 2. 'self' condition; when ASD subject returns proportion of the money.	1. no significant difference 2. Control > ASD; middle cingulate. <i>Reduced cingulate response in ASD group correlates with total, social and communication ADI scores. Controls activate cingulate in both 'self' and 'other' conditions, unless they were playing with a computer in which case they activate in a similar fashion to that seen in ASD subjects here – suggesting dysfunction in self-referential processing in ASD.</i> (ROI analysis)
Critchley (2000)	9:0	37 (7)	102 (15)	Autism, AS	ICD-10, ADI	Age, IQ	Explicit emotion task: indicate via button press if face stimuli are happy/angry or neutral Implicit emotion task: indicate gender via button press (same stimuli).	Emotion vs neutral stimuli ASD > control; left superior temporal gyrus and peristriate visual cortex. Control > ASD; right fusiform cortex. <i>Significant group x condition interaction in cerebellar vermis, left lateral cerebellum, striatum, insula and amygdalohippocampal junction, and middle temporal gyrus.</i>

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Mean age (sd)	Autism group		Diagnostic measures	Control matching criteria	Task design	Main findings
			Mean IQ (sd)	Diagnosis				
Dalton (2005)	1. 11:0	1. 15.9 (4.7)	1. 94 (19.5)	1. Autism, AS	1. DSM-IV, ADI	1. Age, gender	1. Indicate via button press if stimuli emotional or neutral. Happy, fear, anger and neutral face stimuli presented (half quarter turned, half facing ahead); resting baseline.	1. Control > ASD; bilateral fusiform, occipital gyrus and middle frontal gyrus. ASD > control; left amygdala and orbitofrontal gyrus. <i>Differences did not relate to orientation or emotional content. Fixation on eyes correlated with level of activity in left amygdala and right anterior fusiform gyrus in ASD group, effect not seen in controls.</i>
	2. 16:0	2. 14.5 (4.6)	2. 92.1 (27.7)	2. Autism, AS	2. DSM-IV, ADI	2. Age, gender	2. Discriminate familiar and unfamiliar faces via button press; resting baseline.	2. Control > ASD; bilateral fusiform, left anterior medial cortex, left posterior lateral cortex, right occipital cortex. <i>Greater activation in right occipital and fusiform gyrus in control group in response to familiarity, effect not seen in ASD group. Fixation on eyes correlated with level of activity in right amygdala and right anterior fusiform gyrus in ASD group, effect not seen in controls.</i>
Dapretto (2006)	9:1	12.05 (2.5)	96.4 (18.3)	HFA	ADOS, ADI	Age, IQ	Imitation of emotional expressions; observation of emotional expressions; fixation baseline.	Imitation vs rest Control > ASD; bilateral inferior frontal gyrus, insula, periamygdaloid regions, ventral striatum and thalamus. ASD > control; left anterior parietal and right visual association areas. Observation vs rest Control > ASD; bilateral inferior frontal gyrus.

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Mean age (sd)	Autism group		Diagnostic measures	Control matching criteria	Task design	Main findings
			Mean IQ (sd)	Diagnosis				
Deeley (2007)	9:0	34 (10)	114 (12)	AS	DSM-IV, ICD-10, ADI, ADOS	IQ, gender, handedness, task performance	Gender discrimination via button press. Neutral faces; emotional faces (high and low intensity); fixation baseline. 1. Fear vs baseline 2. Disgust vs baseline 3. Happy vs baseline 4. Sad vs baseline 5. Neutral faces (from each emotion condition) vs baseline	1. Control > ASD; right fusiform gyrus and cerebellum and left pre and postcentral gyrus. 2. Control > ASD; left fusiform gyrus, lingual gyrus and cerebellum. 3. Control > ASD; left fusiform gyrus, lingual gyrus and cerebellum. 4. Control > ASD; bilateral fusiform gyrus, lingual gyrus and cerebellum and left inferior occipital gyrus. 5. Control > ASD; fusiform, lingual, occipital cortices and cerebellum. <i>Intensity of emotion had an effect on brain activation at a trend level in both groups which varied with each emotion.</i>
Ditcher (2007)	16:1	22.9 (5.2)	105 (18.6)	14 HFA, 3 AS	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness, education, task performance	1. Indicate via button press direction of central arrow that was congruent (condition1) or incongruent (condition2) with direction of flanker arrows. 2. Indicated via button press direction of eye gaze in central face that was congruent (condition1) or incongruent (condition2) with direction of eye gaze in flanker faces.	1. No significant group difference. 2. Control > ASD; bilateral dorsolateral prefrontal cortex, right inferior frontal/anterior insula cortex, anterior cingulate and bilateral intraparietal sulcus. (ROI analysis)
Frietag (2008)	13:2	17.5 (3.5)	101.2 (21.2)	ASD	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness	Indicate via button press if stimulus is biological motion or scrambled. Point-light walkers; scrambled version; fixation baseline.	1. All motion stimuli vs fixation; no group differences. 2. Biological motion vs scrambled Control > ASD; right middle temporal gyrus, medial and middle frontal gyrus and left anterior superior temporal gyrus, fusiform gyrus, and bilateral post central gyrus and inferior parietal lobule. (uncorrected stats.)

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Gaffrey (2007)	10:0	26.1 (10.5)	101.5 (11.9)	8 autism, 2 AS	DSM-IV, ADI, ADOS	Age, gender, handedness, Non-verbal IQ	Word categorisation (colours, tools and feelings) via button press; letter recognition in strings of non-word letters as baseline condition.	ASD > control; left medial frontal gyrus, middle temporal gyrus, lingual gyrus and cuneus, right lingual gyrus, middle occipital gyrus, post central gyrus, posterior cingulate and precuneus.
Gervais (2004)	5:0	25.8 (5.9)	81 (18.8)	Autism	DSM-IV, ADI	Age, gender	1. Passive listening to vocal sounds; silence as baseline. 2. Passive listening to vocal sounds; environmental sounds as baseline.	1. Control > ASD; right superior temporal sulcus region and bilateral superior temporal gyrus. 2. Control > ASD; right middle temporal gyrus and bilateral superior temporal sulcus region.
Gilbert (2008)	12:3	38 (13)	119 (14)	ASD	ADOS	Age, IQ, task performance	1. Sequenced button press; randomly generated button press as baseline. 2. Press in response to curved letters as progress through alphabet; same task with only start letter presented and thereafter task was stimulus independent.	1. Control > ASD; left cerebellum and left lateral temporal cortex. 2. Control > ASD; medial parietal and occipital cortex.
Gomot (2006)	12:0	13.5 (1.6)	116 (18)	HFA	DSM-IV, ADI	Age, IQ, gender, handedness	Passive auditory stimulation whilst participants watched a video. 1. Novel sounds; standard sounds as baseline. 2. Deviant sounds; standard sounds as baseline.	ASD > control; medial prefrontal cortex, amygdala, cerebellum and other temporal and parietal regions. 1. Control > ASD; bilateral inferior parietal lobe and posterior superior temporal gyrus, right inferior and middle frontal gyrus, left anterior cingulate gyrus and right anterior cerebellum. 2. Control > ASD; left anterior cingulate gyrus, left medial orbitofrontal region and left inferior frontal gyrus. (uncorrected stats)
Hadjikhani (2004a)	11:0	36 (12)	119 (8)	Autism, AS, PDD-nos	DSM-IV, ADI-R, ADOS,	IQ, gender	Passive viewing of neutral faces with fixation cross over eye region; scrambled faces as baseline.	No significant differences between ASD and control group when activation within ROI's compared.
Hadjikhani (2004b)	8	35 (12)	117 (6)	Autism, AS, PDD-nos	ADI-R, ADOS	IQ	Visual checkerboard	No qualitative difference in activation patterns between groups.
Hadjikhani (2007)	8:2	34 (11)	124 (10)	6 autism, 3 AS, 1 PDD-nos	ADI-R, ADOS	Age	Passive viewing of neutral faces with fixation cross over eye region; scrambled faces as baseline.	Control > ASD; right superior temporal sulcus region, somatosensory and premotor cortex, inferior frontal cortex and amygdale. (ROI analysis) <i>Fusiform Face Area activation in ASD group not significantly different from controls.</i>

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Harris (2006)	14:0	36 (12)	116 (8)	7 autism, 5 AS, 2 PDD-nos	DSM-IV, ADI, ADOS	Age, gender, handedness, verbal IQ, task performance	Viewing concrete and abstract words. Perceptual task; upper/lower case discrimination. Semantic task; positive/negative discrimination.	<i>Direct group comparison not performed. ASD group appeared to have greater activation of Wernicke's area and less Broca's area during semantic processing. Control group activation was modulated by word type; an effect not seen in the ASD group.</i>
Herrington (2007)	10:0	27.6 (7.1)	109	AS	DSM-IV, ICD-10	Age, IQ, gender, handedness, task performance	Button press to indicate direction of movement. Point-light walkers; scrambled version; fixation baseline.	1. Scrambled movement vs fixation Control > ASD; right superior temporal gyrus and angular gyrus. 2. Walkers vs fixation Control > ASD; bilateral cerebellum, fusiform gyrus, middle temporal gyrus, middle occipital gyrus, cuneus, right inferior temporal gyrus and inferior occipital gyrus, and left superior temporal gyrus, inferior parietal lobe, angular gyrus, precuneus and precentral gyrus.
Hubl (2003)	7:0	27.7 (7.8)	98 (17)	Autism	ICD-10, ADI, ADOS	Age, IQ, gender, task performance accuracy (not RT)	1. Identify target via button press. Happy, sad, angry and neutral faces presented. Target happy (explicit emotion condition); target female (implicit emotion condition); scrambled faces as baseline condition. 2. Colour counting; shape counting within a mosaic; and a rest condition.	<i>Values from ROIs were extracted from each condition and investigated in an ANOVA for interactions with diagnosis, task, region and hemisphere.</i> <i>Activations for each task were different between ASD and controls. Different tasks activated different regions. The ASD and control groups differ with respect to the difference in activations caused by each task in different regions.</i>
Just (2004)	17	Not reported	> 80	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status	Sentence comprehension (identifying the agent or recipient of the action); fixation baseline.	Control > ASD; left inferior frontal gyrus. ASD > control; left superior/middle temporal gyrus.
Just (2006)	17:1	27.1 (11.9)	109.3 (17.7)	Autism	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	Indicate via button press required number of moves to complete Tower of London task displayed; fixation baseline.	Control > ASD; bilateral inferior and superior parietal lobe, angular gyri, superior and mid occipital cortex, middle frontal gyri, right precentral gyrus, superior frontal and left inferior frontal gyrus. ASD > control; bilateral hippocampus and thalamus and left lingual gyrus.

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Kana (2006)	11:1	22.5 (8.8)	110.7 (9.2)	Autism	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	1. Indicate via button press whether a low-imagery sentence is true or false; fixation baseline. 2. Indicate via button press whether a high-imagery sentence is true or false; fixation baseline.	1. ASD > control; left intraparietal sulcus, right superior parietal lobe, bilateral cuneus, precuneus and lingual gyrus. 2. Control > ASD; left inferior frontal gyrus, left angular gyrus and left middle frontal gyrus.
Kana (2007)	11:1	26.8 (7.7)	110.1 (12.6)	HFA	ADI, ADOS	Age, IQ, gender, handedness, socioeconomic status	1. Instructed to inhibit button press response to letter A (but A never presented); fixation baseline. (Control task) 2. Instructed to inhibit button press response to letter A; fixation baseline. 3. Inhibition and working memory task (don't press if same letter repeated); fixation baseline.	1. No significant differences between groups. (Groups task performance matched). 2. Control > ASD; right insula, inferior frontal gyrus, cingulate gyrus and premotor cortex. (Groups task performance matched) 3. Control > ASD; left anterior cingulate gyrus and precuneus and right angular gyrus ASD > control; bilateral premotor cortex. (Groups not task performance matched.)
Kleinmans (2008)	19:0	23.5 (7.8)	106.7 (15.7)	8 autism, 9 AS, 2 PDD-nos	DSM-IV, ADI-R, ADOS	Age, IQ, task performance	1-back with neutral faces; 1-back with houses as baseline.	No significant group differences.
Koshino (2005)	13:1	25.7	100.1	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	n-back task (0,1,2); fixation baseline.	Control > ASD; left dorsolateral prefrontal cortex, inferior frontal gyrus, posterior precentral sulcus and inferior parietal lobe. ASD > control; right inferior frontal gyrus, inferior parietal lobe and bilateral temporal lobe. (ROI analysis and no spatial normalisation)
Koshino (2008)	11:0	24.5 (10.2)	104.5 (13.1)	HFA	ADI-R, ADOS	Age, IQ, gender, socioeconomic status, task performance	0, 1 and 2-back working memory task with face identity; fixation baseline.	Control > ASD; left inferior prefrontal and right posterior temporal cortex. <i>Different location of the Fusiform Face Area within the fusiform gyrus in ASD group compared to controls.</i>
Lee (2007)	12:5	10.37 (1.52)	109.3 (14.2)	8 HFA, 9 AS	DSM-IV, ADI-R, ADOS	Age, IQ, task performance	Embedded figures task; shape matching task as baseline.	No significant group differences. <i>Qualitative difference in activation maps between groups; ASD group failed to recruit medial and lateral prefrontal cortex, ventral temporal cortex and inferior parietal cortex; parietal and occipital activation was bilateral in control group and unilateral in the ASD group.</i>

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Mean age (sd)	Autism group		Diagnostic measures	Control matching criteria	Task design	Main findings
			Mean IQ (sd)	Diagnosis				
Luna (2002)	9:2	32.3 (9.3)	102.7 (12.1)	Autism	ADI, ADOS	Age, IQ	1. Visually guided saccades; fixation baseline. 2. Ocularmotor delayed response task; visually guided saccades.	1. No group differences. (Groups task performance matched) 2. Control > ASD; bilateral dorsolateral prefrontal cortex and posterior cingulate cortex. (Groups not task performance matched, ROI analysis) No significant differences between groups.
Manjaly (2007)	12	14.4 (2.7)	110.1 (20)	3 HFA, 9 AS	DSM-IV, ICD-10, ADI-R, ADOS	Age, IQ, gender, handedness, task performance	Embedded figures task; visuospatial control task as baseline.	<i>Qualitative difference in activation maps between groups; more activation in ASD group in extrastriate cortex and calcarine sulcus than controls.</i>
Mason (2008)	17:1	26.5	101.9	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status, race	Read short scenarios and answered yes/no comprehension questions via button press. Intentional, emotional and physical sentences; fixation baseline.	ASD > control; right middle temporal gyrus, superior temporal gyrus, angular gyrus and supramarginal gyrus. <i>Whilst the recruitment of these regions was modulated by sentence type in the control group (greater activation when making mentalistic inferences) the ASD group recruited these regions for all sentence types.</i>
Muller (2001)	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness, task performance	Visually paced motor response; passive viewing of visual stimuli.	Control > ASD; contralateral sensorimotor cortex and anterior temporal lobe including anterior insula and caudate. ASD > control; bilateral parieto-occipital and contralateral prefrontal cortex.
Muller (2003)	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness,	1) Image of hand with dot indicating appropriate button press for a 6-digit repeated sequence; single-digit stimuli as baseline. 2) Image of hand with dot indicating appropriate button press for a 6-digit repeated sequence; regular 6-digit sequence as baseline.	1) Control > ASD; bilateral occipital and superior parietal cortex and right middle frontal gyrus. ASD > control; bilateral parietal lobes, premotor cortex, right medial frontal area and left middle and superior frontal gyri. 2) Control > ASD; bilateral premotor, superior parietal anterior inferior parietal, temporo-occipital cortex and left anterior cerebellum. ASD > control; frontal cortex anterior to premotor cortex and inferior and posterior parietal cortex.

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Mean age (sd)	Autism group		Diagnostic measures	Control matching criteria	Task design	Main findings
			Mean IQ (sd)	Diagnosis				
Muller (2004)	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness	Image of hand with dot indicating appropriate button press for a 8-digit repeated sequence; single-digit stimuli as baseline.	'late learning' vs 'early learning' Control > ASD; prefrontal cortex. ASD > control; right pericentral and premotor cortex.
Ogai (2003)	5	21.8 (5.9)	112.4 (10.5)	HFA	DSM-IV	Age, IQ, socioeconomic status, education, emotion label task performance	Instructed to think about the emotion being expressed. 1. Happy faces; neutral faces 2. Fear faces; neutral faces 3. Disgust faces; neutral faces	1. No significant difference between groups. 2. Control > ASD; left middle frontal gyrus. 3. Control > ASD; left insula, left inferior frontal gyrus and left putamen.
Oktem (2000)	9	12 (3.1)	76.78	AS	DSM-IV	Age, handedness	Instructed to think over general comprehension questions; rest as baseline.	Control > ASD; frontal lobe.
Pelphrey (2005)	9:1	23.2 (9.9)	107 (16)	Autism	ADI, ADOS	Age, IQ, task performance	Button press in response to shifts in eye gaze that were congruent with the location of a visual stimulus; incongruent trials.	<i>Group x condition contrast; posterior superior temporal sulcus region activity modulated by congruence in control group but not in ASD group. Inferior frontal gyrus and insular cortex modulated by congruence in ASD group but not control group.</i>
Pelphrey (2007)	6:2	24.5 (11.5)	120 (9)	Autism	ADI, ADOS	Age, IQ, task performance	Button press in response to face stimuli. Static neutral; static emotional (anger and fear); dynamic neutral (identity morph); dynamic emotional (emotion morph) events. Fixation baseline.	1. Dynamic emotional condition vs fixation baseline Control > ASD; right amygdala and superior frontal gyrus, left fusiform gyrus and medial frontal gyrus and bilateral middle temporal gyrus. 2. Dynamic emotional condition vs static emotion <i>Group x condition contrast; control group modulate activity in amygdala, superior temporal sulcus region and fusiform gyrus, an effect not seen in ASD group.</i> 3. Dynamic neutral condition vs static neutral No group differences. 4. Static emotion condition vs fixation baseline ASD > control; superior temporal sulcus region. (No amygdala or fusiform gyrus differences) (ROI analysis)

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Pierce (2001)	7:0	29.5 (8)	83.7 (10.9)	Autism	DSM-IV, ADI-R, ADOS, CARS	Age, gender, handedness, task performance	Button press in response to target. Neutral face perception; shape perception.	Control > ASD; bilateral fusiform and left amygdala. (ROI analysis, but findings supported by whole brain within group maps.) No significant between group differences.
Pierce (2004)	8:0	27.1 (9.2)	80.3 (17.7)	Autism	DSM-IV, ADI, ADOS	Age, gender, handedness, task performance	Gender discrimination via button press with familiar and stranger faces; fixation baseline.	
Pierce (2008)	9:2	9.9 (2.1)	108.5 (12.6)	9 autism, 1 AS, 1 PDD-nos	ADI, ADOS	Age, gender, handedness, task performance	1-back task. Button press if stimuli repeated. Familiar adult; stranger adult; familiar child; stranger child; objects; fixation baseline.	No between group differences reported in whole brain analysis. Stranger faces vs baseline Control > ASD; left fusiform. Familiar children vs baseline Control > ASD; posterior cingulate. (ROI analysis)
Piggot (2004)	14:0	13.1 (2.5)	112 (15.9)	7 autism, 7 AS	DSM-IV, ADI, ADOS	Age, IQ, handedness, socioeconomic status, task performance accuracy (but not RT)	1. Match target by emotion to one of two response options. Fearful, surprised and angry face stimuli; shape matching as baseline. 2. Label emotion given two text choices. Fearful, surprised and angry face stimuli; shape matching as baseline.	1. Control > ASD; average fusiform gyrus. (ROI analysis.) 2. No significant group differences.
Pinkham (2008)	12:0	24.08 (5.71)	110 (10.91)	HFA	DSM-IV, ADI, ADOS	Age, gender, handedness, verbal IQ	Indicate judgement of face stimuli via button press. Trustworthiness; age; fixation baseline.	1. Trust vs baseline Control > ASD; right amygdala and Fusiform Face Area and left ventrolateral prefrontal cortex. 2. Age vs baseline ASD > control; left superior temporal sulcus region, right ventrolateral prefrontal cortex. 3. Trust vs age <i>Comparison of within group maps; amygdala, superior temporal sulcus region and ventrolateral prefrontal cortex activity modulated in control group, effect not seen in ASD group.</i> (ROI analysis.)

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Ring (1999)	4:2	26.3 (2.1)	108.5 (10.5)	Autism, AS	DSM-IV, ICD-10	Age, IQ, handedness, socioeconomic status, education, task performance	Embedded figures task; fixation baseline.	Control > ASD; bilateral parietal regions and occipital cortex and right dorsolateral prefrontal cortex. ASD > control; right occipital cortex extending into inferior temporal gyrus.
Schmitz (2006)	10:0	38 (9)	105 (14)	2 HFA, 8 AS	ICD-10, ADI	Age, IQ, gender, handedness, task performance	1. Motor inhibition; motor response. (GO/NO-GO task) 2. Spatial STROOP task. Incongruent events; congruent events. 3. SWITCH task. Events where the rule switched; events where the rule was repeated.	1. ASD > control; left middle/inferior and orbitofrontal gyrus. 2. ASD > control; left insula. 3. ASD > control; right inferior and left mesial parietal cortex.
Schmitz (2008)	10:0	37.8 (7)	107 (9)	3 HFA, 7 AS	ICD-10, ADI	Age, IQ, gender, handedness, socioeconomic status, education, task performance	Continuous performance task with target identification events. Targets associated with monetary reward; targets with no associated monetary reward.	ASD > control; left anterior cingulated gyrus.
Schultz (2000)	14:0	23.8 (12.4)	109.1 (19.5)	8 HFA, 6 AS	ICD-10, ADI-R, ADOS, Vineland	Age, IQ, task performance	Same/different discrimination via button press. Neutral faces, objects; patterns.	Faces vs patterns Control > ASD; right fusiform gyrus ASD > control; bilateral inferior temporal gyrus activation. No differences between groups in object task. (ROI analysis)
Shafritz (2008)	16:2	22.3 (8.7)	102.5 (17.6)	Autism	DSM-IV, ADI, ADOS	Age, IQ	Button press in response to targets; non-targets as baseline. Targets were maintained or shifted between runs.	Control > ASD; dorsolateral prefrontal cortex, basal ganglia and insula.
Silk (2006)	7:0	14.7 (2.9)	114 (16.9)	Autism, AS	DSM-IV, ADI-R	Age, IQ, gender, handedness	Mental rotation and matching of shapes; shape matching as baseline.	(Stats uncorrected) Control > ASD; right inferior and medial frontal gyri including caudate and dorsal premotor cortex.

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Takarae (2007)	13	24.5 (7.7)	105.9 (12.3)	Autism	DSM-IV, ADI, ADOS	Age, IQ	1. Visually guided saccades; fixation baseline. 2. Smooth pursuit of a visual target; fixation baseline.	1. Control > ASD; bilateral frontal and supplementary eye fields, posterior parietal cortex and cerebellum. ASD > control; bilateral dorsolateral prefrontal cortex, anterior and posterior cingulate cortex, medial thalamus, caudate nucleus and right dentate nucleus. 2. Control > ASD; bilateral frontal eye fields, posterior parietal cortex, posterior cingulate cortex, cingulate motor area, cerebellum, dorsolateral prefrontal cortex, precuneus and pre-supplementary motor area.
Thakkar (2008)	10:2	30 (11)	114 (9)	8 autism, 2 AS, 2 PDD-nos	DSM-IV, ADI, ADOS	Age, verbal IQ, gender, handedness, socioeconomic status, education	Pro-saccade and anti-saccade events; fixation baseline.	1. Error vs correct events Control > ASD; right medial superior frontal gyrus. 2. Correct responses vs fixation ASD > control; right rostral anterior cingulate gyrus.
Wang (2004)	12:0	12.2 (4.8)	Not reported	Autism, AS, PDD-nos	ADI, ADOS	Age, gender, handedness, nonverbal language age, task performance	1. Match target by emotion to one of two response options. Fearful and angry face stimuli; shape matching as baseline. 2. Label emotion given two text choices. Fearful and angry face stimuli; shape matching as baseline.	1. Control > ASD; bilateral fusiform gyrus. ASD > control; precuneus. 2. No significant group differences. (ROI analysis)
Wang (2006)	18:0	11.9 (2.8)	102 (18)	Autism, AS	ADI, ADOS	Age, IQ, gender, handedness, social responsiveness scale	Participants listen to scenarios and indicate via button press if the speaker means what they say. 1. Event knowledge and prosodic cues; resting baseline. 2. Event knowledge only; resting baseline. 3. Prosodic cues only; resting baseline.	1. ASD > control; left pre-central gyrus and bilateral inferior frontal gyrus. 2. Control > ASD; left superior frontal gyrus ASD > control; left pre and post-central gyrus, superior temporal gyrus, superior temporal sulcus region and medial temporal gyrus and right inferior frontal gyrus. 3. ASD > control; left superior temporal sulcus region and right temporal pole.

Emotion Processing in Autism Spectrum Disorder

Study (year)	N (M:F)	Autism group			Diagnostic measures	Control matching criteria	Task design	Main findings
		Mean age (sd)	Mean IQ (sd)	Diagnosis				
Wang (2008)	18:0	12.4 (2.9)	98 (17)	ASD	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness, social responsiveness scale, task performance	<p>Indicate via button press if the speaker is sincere or not. Storyboards and speech stimuli.</p> <p>1. Participants asked to pay attention; resting baseline.</p> <p>2. Participants asked to pay attention to facial expression or tone of voice; resting baseline.</p> <p>3. All ironic scenarios; non-ironic scenarios.</p>	<p>1. Control > ASD; bilateral medial prefrontal cortex, superior temporal gyrus and cerebellum.</p> <p>2. Control > ASD; superior temporal gyrus, cerebellum and visual cortex.</p> <p>3. Control > ASD; bilateral temporal regions and medial prefrontal cortex.</p>
Williams (2006)	16:0	15.4 (2.24)	100.4 (21.7)	ASD	ADI, ADOS	Age, IQ, gender	<p>Passive viewing task. Hand with index or middle finger raised; hand stimuli with cross on middle or index finger; cross on left or right side of screen; resting baseline.</p> <p>Hand with index or middle finger raised (imitation); hand stimuli with cross on middle or index finger (execution); cross on left or right side of screen (execution); resting baseline.</p>	<p>Imitation vs rest Control > ASD; right fusiform gyrus, middle occipital gyrus, lingual gyrus, middle temporal gyrus and bilateral inferior parietal lobe, and greater activation in right parahippocampal gyrus and cingulate gyrus, left uncus, precentral gyrus, claustrum, middle frontal gyrus, middle occipital gyrus and bilateral superior temporal gyrus.</p> <p>Imitation vs execution Control > ASD group had less activation in right precuneus, left anterior cingulate and inferior parietal lobe. ASD > control; left superior parietal lobe and bilateral precentral gyrus and middle frontal gyrus. (ROI analysis)</p> <p><i>ROI of Mirror Neuron System; ASD group activated anterior parietal lobe and somatosensory cortex less than the control group in response to both imitation and action execution. Left amygdala activity was modulated in the control group by task conditions; activity in this region was significantly less variable in the ASD group.</i></p>

Table 2.1 – Summary table of papers included in the review. The main findings reported are significant differences in a whole brain between group contrast unless detailed in italics or otherwise stated. Abbreviations; ADI-R – Autism Diagnostic Interview-Revised
 ADOS – Autism Diagnostic Observational Schedule, AQ – Autism Quotient, AS – Asperger Syndrome, DSM-IV - Diagnostic and Statistical Manual of Mental Disorders – 4th edition, HFA – High Functioning Autism, ICD-10 - International Classification of Diseases – 10th edition, IQ – Intelligence Quotient, PDD-nos – Pervasive Developmental Disorder – not otherwise specified, ROI – Region Of Interest.

Behavioural investigation of visual processing tasks such as the Embedded Figures Task have found enhanced performance in ASD which has been attributed to a cognitive style in which component parts are focused on more closely than the general context, described as having weak central coherence. Whilst the study by Ring et al (1999) was potentially underpowered (investigating only 6 ASD participants) and applied an unconstrained baseline condition of fixation on a blank screen, differences in processing style on a neural level were reported in ASD whilst participants completed the Embedded Figures Task. The ASD group showed less activation in dorsolateral prefrontal cortex, indicating less reliance on working memory to carry out the task. Instead the ASD group appeared to rely more heavily on mental imagery and object perception, activating occipito-temporal brain regions significantly more than controls. More recently, this task has been employed by Manjalay et al (2007) and Lee et al (2007) in larger cohorts of adolescent participants, using a closely matched control condition. Whilst within group maps suggested a more object perception based strategy was adopted by the ASD group (more extrastriate activation) no significant between group differences were reported by Manjalay et al (2007) or Lee et al (2007). In a study investigating visual perception using a shape counting and a colour counting task there is further support for the idea that in autism there is heavier reliance on visual search for successful task completion (Hubl et al., 2003).

To test the hypothesis further that people with ASD use a more visually based style of cognition, studies of mental imagery have been conducted. Silk et al (2006) asked participants to perform a task where the mental rotation of an object was required and it was then matched to a target. When contrasted with a matching task without a mental rotation component, the ASD group engaged frontal cortex extending into caudate and premotor areas in the right hemisphere less than the control group. Kana et al (2006) went further to see if mental imagery was a strategy recruited differently in autism when processing sentences. Contrasting high and low-imagery sentences with fixation baseline, Kana et al (2006) reported group differences which indicated that in the high-imagery condition the ASD group recruited regions associated with verbal processing and rehearsal (left inferior frontal gyrus, angular gyrus and middle frontal gyrus) less than

controls. In the low-imagery condition, the ASD group had significantly more activity than controls in regions associated with visual processing. This study provides further support that even within a task of lexical comprehension participants with ASD tend to recruit a more visual processing strategy.

Further evidence comes from Koshino et al (2005) who used the n-back task to specifically address the issue of working memory in autism. They found reduced dorsolateral prefrontal cortex, inferior frontal gyrus, posterior precentral sulcus and inferior parietal lobe activity in the left hemisphere in the ASD group relative to controls alongside a comparative over-activation of parietal and temporal regions. These findings were interpreted to support a greater reliance on visuo-spatial regions for the autistic participants to complete the task, as they recruited visual coding regions more, and verbal coding and working memory regions less, than control participants. Koshino and colleagues replicated their finding of reduced left prefrontal cortical activation in ASD relative to controls in a later study, employing a task of working memory that used face instead of letter stimuli (Koshino et al., 2008).

There is also evidence to suggest that this difference extends into spatial working memory tasks. Luna et al (2002) isolated working memory by contrasting two ocular motor tasks. The first was a simple task of visually guided saccades and the second involved a delay between the target being shown to participants and their response, incorporating working memory demands. Whilst the first task showed no between group differences, in the second task a relative hypoactivation in the ASD group was found in bilateral dorsolateral prefrontal cortex and posterior cingulate in an ROI analysis of working memory circuitry. However, differences in brain activation in these regions between ASD and control groups have been reported in studies using simple sensorimotor tasks - visually guided saccades (with no working memory component) and smooth pursuit of a visual target (Takarae et al., 2007). These findings make it less clear whether group differences reported by Luna et al (2002) are indicative of a working memory dysfunction or in fact the manifestation of differences which relate to sensorimotor control.

Cumulatively, there are findings from a variety of task types to suggest that areas of the prefrontal cortex generally recruited for executive functions are activated to a lesser extent in ASD. More weight is however given to visual and perceptual systems. Whilst it is not obvious how a visually predisposed cognitive style relates to the core clinical features of autism it is interesting to note that the only evidence based and most commonly adopted approaches used to teach children with autism rely heavily on the use of visual supports. In establishing basic requesting skills in non-verbal children with autism, the Picture Exchange Communication Systems has been found to be effective (Bondy 2001) and is commonly implemented by Speech and Language Therapists in schools across the UK. In classrooms, the TEACCH approach (Treatment and Education of Autistic and related Communication handicapped Children) has been found to be an effective method for working with children with autism (Probst and Leppert, 2008) and relies on a range of visual measures (visual timetables, start/finish boxes, timers) to support children with autism through their school day. It may be that the effectiveness of these strategies at least in part is due to the fact that they capitalize on the naturally visual cognitive style of people with autism.

2.3.3.2 Face processing

As social deficits are a core feature of ASD and much social information during everyday communication is conveyed within faces, it is unsurprising that face processing has attracted a lot of attention in the fMRI investigation of ASD. Behavioural evidence exists to suggest that individuals with ASD fail to demonstrate the ‘inversion effect’ when processing faces i.e. a decrease in face processing task performance when faces are presented upside down. Shultz et al (2000) hypothesized that this may be due to a lack of expertise in ASD participants in processing faces and so they therefore process face stimuli in a manner similar to object processing which is “typically reliant on the detection of individual features” and therefore less susceptible to the inversion effect. It was also proposed that this reduced inversion effect in ASD may be accounted for by a more general deficit in configural processing regardless of expertise, a tendency to process all stimuli by component features as if it were an object. In either case, Shultz et al (2000) hypothesized that the ASD group would recruit a neural network generally reserved for object processing when responding to face stimuli. Due to this specific

hypothesis, an ROI analysis of face related brain regions; the fusiform gyrus and the inferior temporal gyrus, and object related brain regions; lateral occipital gyrus and parahippocampal gyrus, was carried out. No group differences were reported in the object processing task. However in the face processing task the ASD group had significantly more inferior temporal gyrus activation than the control group and the control group had significantly more activation in the right fusiform gyrus. This supports the hypothesis that in ASD the neural network recruited to process faces is more akin to that used for object processing. It is not possible to ascertain from this study whether this was due to the lack of development of face specific expertise in the ASD group or a more general dysfunction of configural processing.

This point was addressed by Pierce et al (2001). Within this study, not only was the finding of reduced fusiform activation in ASD relative to controls in response to face stimuli replicated (and in this instance found to be a bilateral hypoactivation), but they went further to investigate the individual-specific sites of maximal activation. Previously, in control populations, a region of the fusiform gyrus has been shown to respond specifically to face stimuli and is so referred to as the fusiform face area (FFA) (Haxby et al., 2002). This same region has been shown however to activate in response to stimuli other than faces, for example when pictures of cars are shown to motor enthusiasts (Gauthier et al., 2000). This evidence suggests that the FFA may respond to stimuli for which specialization has occurred in response to experiential factors. It was suggested by Pierce et al (2001) that maximal activation out-with the FFA in the ASD group would indicate that their object processing style of face stimuli is a result of a lack of developed expertise in the processing of faces. In support of this hypothesis, whilst the control group all demonstrated foci of maximal activation within the fusiform gyrus, regions of maximal activation in the ASD group varied widely including frontal lobe and cerebellum. Pierce and colleagues addressed the issue of experiential factors more specifically in a later study. Using an event-related design, participants were asked to make gender discrimination decisions on face stimuli, half of which were personally familiar and the other half were strangers. Whilst there were qualitative differences in the ASD and control groups maps, between group analysis failed to find any significant

differences in activation in contrasting familiar faces with fixation baseline, stranger faces with fixation baseline or familiar faces with stranger faces. In fact, even with an ROI analysis, no significant group differences in fusiform activation were found and task related modulations in brain activity observed in the control group were seen in the ASD group; right fusiform gyrus activity > left fusiform gyrus activity, familiar > stranger activation (Pierce et al., 2004). In a later study, children with ASD were investigated using a task in which the familiar/stranger condition was subdivided further into children and adult stimuli (Pierce and Redcay, 2008). Again, no significant differences between groups was reported from the whole brain analysis, but in an ROI analysis, activation was significantly reduced in the left fusiform gyrus in the ASD group in response to stranger adult faces.

Dalton et al (2005) also investigated the effect of face familiarity on brain activation in ASD. In this study, participants were explicitly asked to discriminate between whether the face presented to them was familiar or unfamiliar. Behaviorally, the ASD group was less accurate at this than the control group and eye gaze data showed that the ASD group also spent significantly less time fixating on the eyes of stimuli. Additionally, fMRI data demonstrated that the ASD group had less activation in bilateral fusiform, left anterior medial cortex, left posterior lateral cortex and right occipital cortex than the control group during this task. A further ROI analysis revealed that the ASD group had greater activation of the right amygdala than the control group. Time spent fixating on eyes correlated with level of activity in right amygdala and right anterior fusiform gyrus in the ASD group, an effect not seen in controls. In contrast to the earlier study (Pierce et al., 2004) whilst the familiar face condition resulted in greater activation in right occipital and fusiform cortex when contrasted with the unfamiliar condition in the control group, this effect was not seen in ASD group.

Differences in scan path and the features focused on by individuals with ASD had been reported in the behavioural literature in addition to the study by Dalton et al (2005). It was hypothesized that the reports of hypoactivation of typical face processing brain regions in ASD was a result of ASD participants processing faces in a different manner

and not necessarily representative of a difference in the functional neuroanatomy of people with autism. Hadjikhani et al (2004a) developed this line of behavioural evidence in their fMRI study of basic face processing in autism. Study participants were asked to passively view face stimuli (with scrambled versions used for the baseline condition) but their attention was directed to the eye region with the addition of a red fixation cross. When activation of various face processing ROI's (fusiform gyrus, inferior occipital gyrus, superior temporal sulcus region and inferior temporal gyrus) was compared between groups, no significant differences in activation were found and comparable levels of fusiform activation in response to faces was reported in ASD and control participants. One limitation of this study was that data was only collected in occipital lobe, parietal lobe and the posterior and middle portions of the temporal lobe, which precluded a whole brain analysis. In a further study by this group, using the same task but acquiring data across the whole brain, the original finding of FFA activation in the ASD group which did not differ significantly from the control group was replicated. This finding has also been confirmed by an independent group (Bird et al., 2006). However hypoactivation in the extended network associated with the processing of social stimuli was reported by Hadjikhani et al (2007). Specifically, the ASD group showed significantly reduced activation of the superior temporal sulcus region, somatosensory cortex, premotor cortex, inferior frontal cortex and the amygdala.

Activation across social brain networks in response to face stimuli has also been investigated during more cognitively demanding working memory tasks with reports of aberrant recruitment of social brain regions (Koshino et al., 2008) and brain activation which did not differ from controls (Kleinmans et al., 2008). Fusiform gyrus activation did not differ significantly between the ASD and control group in either of the above studies.

In summary it would appear that despite some early reports of hypoactivation of the fusiform gyrus during face processing in autism, there are now in fact more reports of typical fusiform gyrus function in autism. For this to be achieved however, tasks have been designed to incorporate cues to ensure participants engage with the face stimuli and attend to the salient features of faces such as eyes. It would seem that perhaps it is

abnormal function in the more extended network that is responsible for the processing of socially relevant stimuli more generally that is dysfunctional in autism, rather than a face specific issue. Evidence from prosopagnosic patients supports this, where lesions to the fusiform gyrus produce much more severe deficits in relation to face processing than the relatively subtle deficits reported in ASD (Takahashi et al., 1995).

2.3.3.3 Emotional face processing

A further subset of the literature has focused on face processing, but with the added element of emotion. Hubl et al (2003) reported reduced fusiform gyrus activity in the ASD group relative to controls in an emotional face processing task. Emotional and neutral face stimuli were used in the same condition with task demands altering between conditions i.e. whether attending to emotion is implicit or explicit. Therefore within the analysis reported it is difficult to interpret whether group differences relate to face processing, the emotional content of the stimuli or the implicit/explicit processing of emotion.

Piggot et al (2004) investigated a group of adolescents with ASD using both a perceptual (matching) and linguistic (labeling) task involving emotional face stimuli. This was contrasted with a shape matching task so again, although the task involved faces expressing emotion (fear, surprise and anger), the component of emotion processing was not isolated from face processing. In the perceptual task, where participants had three emotional faces to process, the ASD group had significantly less activation in the fusiform gyrus (averaged across hemispheres) than the control group, as identified in an ROI analysis. Amygdala and prefrontal cortex activation did not differ between groups. No group differences were identified in the emotion label task. The same tasks (with the exclusion of 'surprise' stimuli) were employed by Wang et al (2004) on a similar cohort of adolescents. Again, an ROI analysis revealed no group differences in the emotion label task but bilateral fusiform hypoactivation in the ASD group in the emotion match task. A relative hyperactivation was seen in the ASD group bilaterally in the precuneus in this task. Further to this, when differences in activation were compared between tasks, the control group exhibited greater amygdala activation during the more perceptual

matching task than in the labeling task. This was an effect not seen in the ASD group, suggesting that amygdala activation is less well modulated in the ASD group in response to task demands.

In an event-related design, Dalton et al (2005) presented happy, fearful, angry and neutral face stimuli (half quarter turned, half facing ahead) and asked participants to indicate by button press if the face presented was emotional or neutral. The ASD group performed less accurately at this task and eye gaze data showed that they also spent significantly less time than controls fixating on the eye region of face stimuli. During this task, the ASD group activated bilateral fusiform, occipital gyrus and middle frontal gyrus less than the control group. Greater activation relative to controls was seen in the left amygdala and orbitofrontal gyrus. No interactions were seen in relation to the orientation of face stimuli or their emotional content. However, time spent fixating on the eye region of face stimuli correlated with level of activity in left amygdala and right anterior fusiform gyrus in the ASD group, an effect not seen in the control group.

Ashwin et al (2007a) designed a task to investigate brain activation in response to faces in ASD, with an added element to investigate the modulation of the social brain network in response to the intensity of emotion. When contrasting face stimuli (including neutral faces and faces expressing low and high intensities of fear) with scrambled face stimuli in an ROI analysis of the social brain, the ASD group demonstrated a reduced engagement of the left amygdala and left orbitofrontal cortex. The ASD group had greater activation than controls in right anterior cingulate cortex and bilateral superior temporal cortex. Further to this, the level of intensity of fear expressed in the face stimuli modulated activity in bilateral amygdala, fusiform gyrus, right medial prefrontal cortex and superior temporal sulcus region in the control group, an effect not seen in the ASD group.

Deeley et al (2007) also examined the effect of emotion intensity on brain activation in ASD but investigated this across a range of emotions; fear, disgust, happiness and sadness. Positive trends of neural responses to the level of intensity of emotion were seen in both groups in response to happy and fearful stimuli and to disgusted stimuli in the

control group only. In neither group were trends found between neural responses and the intensity of sad stimuli. However, in a whole brain analysis of each face condition contrasted with fixation baseline, reduced activation in the ASD group relative to controls was reported in bilateral fusiform gyrus in addition to lower activation of occipital and lingual cortex and cerebellum. These group differences were reported in contrasts of both high and low intensities of emotion and across the range of emotions investigated. Furthermore, this reduced activation in the ASD group was seen when the neutral face condition was contrasted with fixation baseline.

By contrasting blocks of emotional face stimuli (happy and angry) with blocks of neutral faces, Critchley et al (2000) attempted to look at differences in ASD and control groups' brain activation in response to the component of emotion. The ASD group had more activity in the left superior temporal gyrus and peristriate visual cortex and less in right fusiform cortex than the control group. Critchley et al (2000) also manipulated task demands to explore differences between groups if the emotional content was explicitly attended to by participants (emotion label) or not (gender label). This resulted in a significant group by condition interaction in cerebellar vermis, left lateral cerebellum, striatum, insula, amygdalohippocampal junction and middle temporal gyrus. It should be noted however that the ASD group were not performance matched to the control group in the explicit emotion label task which may confound results. Also, the task that was employed asked participants to indicate if the face was happy/angry or neutral but stimuli were presented in blocks of emotional or neutral faces making the need to explicitly attend to the emotion in each stimulus questionable.

Ogai et al (2003) isolated the processing of emotion by contrasting happy, fearful and disgusted faces with neutral faces. Whilst the number of participants investigated was small (n=5) and the exact nature of the analysis somewhat unclear, reduced activation in the ASD group relative to the control group was reported that was also specific to the type of emotion presented. Whilst no group differences were seen in the task using happy face stimuli, in the fear task reduced activation in the ASD group was found in the left

middle frontal gyrus. The greatest differences were seen in the disgust task; the ASD group had reduced activation in left insula, left inferior frontal gyrus and left putamen.

Again, as in the studies of neutral face processing, there is evidence both for and against fusiform gyrus dysfunction in autism, which also seems to vary depending on the exact task demands. Few of the studies designed paradigms which in fact isolated the processing of emotion however the ones that did generally report differences in brain regions thought to be responsible for emotion processing in the ASD group relative to controls.

2.3.3.4 Motion in relation to social stimuli

Another aspect of face and emotion processing is the temporal component of the stimuli. Whilst the studies discussed so far have employed static stimuli a more environmentally valid stimulus set would include dynamic representations of emotion, such as used by Pelphrey et al (2007). In addition to both neutral and emotional (fear and anger) static face stimuli, dynamic face stimuli which morphed from one identity to another in neutral events, and from one emotion to another in emotion events were used. When emotional morph events were contrasted with fixation baseline, the ASD group was found to activate right amygdala and superior frontal gyrus, left fusiform gyrus and medial frontal gyrus and bilateral middle temporal gyrus less than the control group. The contrast of emotional morphs with static emotional stimuli revealed that in the control group activity in the amygdala, superior temporal sulcus region and fusiform gyrus was modulated by the element of motion; an effect not seen in the ASD group. However, task modulation was observed in visual cortex in a region associated with the processing of human motion (human analog of MT/V5), a region not included in the social brain network, in both groups. These findings were restricted to the contrasts involving emotional stimuli as group differences were not seen when activation to neutral static or morphed stimuli were analysed. When activation to static emotion stimuli was investigated, an ROI analysis revealed no group differences in amygdala or fusiform activation but greater activation of the superior temporal sulcus region in the ASD group. This led the authors to suggest that aberrant activation of social brain regions in ASD is specific to dynamic emotion.

Whilst this seems in contrast with some previous reports of hypoactivation in ASD cohorts in response to static displays of faces, it may be that group differences were sub-threshold with neutral and static face stimuli and the effect is more robust using these more salient and environmentally valid stimuli like dynamic emotion morphs.

Studies have also been designed to specifically address the processing of movement from social stimuli i.e. biological motion (Freitag *et al.*, 2008, Herrington *et al.*, 2007). In the first of these studies, qualitative differences in activation patterns in ASD and control groups were reported in response to motion stimuli contrasted with fixation baseline. However significant between group differences were seen when biological motion stimuli were contrasted with scrambled versions of the same stimuli. In this contrast the ASD group activated right middle temporal gyrus, medial and middle frontal gyrus, left anterior superior temporal gyrus and fusiform gyrus, and bilateral post central gyrus and inferior parietal lobule less than the control group (Freitag *et al.*, 2008). In the second study, whilst the contrast of scrambled movement with fixation baseline revealed hypoactivation in the ASD group in the right superior temporal gyrus and angular gyrus, the contrast of biological motion vs fixation identified a much more extensive network of hypoactivation in the ASD group. This included bilateral cerebellum, fusiform gyrus, middle temporal gyrus, middle occipital gyrus and cuneus, right inferior temporal gyrus and inferior occipital gyrus, and left superior temporal gyrus, inferior parietal lobe, angular gyrus, precuneus and precentral gyrus (Herrington *et al.*, 2007). This provides evidence that in ASD, the brain processes movement in a different way but particularly when the movement conveys information that is socially relevant.

2.3.3.5 Eye gaze

Another important social cue is that of eye gaze. Pelphrey *et al* (2005) used an event related paradigm in which participants observed a cartoon face which shifted eye gaze in the direction of the appearance of a visual stimulus in congruent trials and to a different location during incongruent trials. As previously found in control populations, the control group in this study had increased activation in posterior superior temporal sulcus during incongruent trials compared to congruent trials. This congruence modulation was

not observed in the ASD group although the superior temporal sulcus region did activate in response to shifts in eye gaze. This suggests that whilst on a basic visual level the stimuli are processed in a typical way in the ASD group, subtle modulations of this activity based on whether the direction of eye gaze meets with predictions based on context is missing. Increased activation of inferior frontal gyrus and insular cortex was seen in the ASD group in the contrast of congruence however, suggesting that this feature of the stimuli is processed in the ASD group, but in an atypical way.

Dichter et al (2007) isolated the dysfunction of systems processing eye gaze congruence using a task in which central face stimuli in a field of five had eye gaze in a direction congruent or incongruent to flanker face stimuli. Using an ROI analysis, circuitry subserving cognitive control was found to be modulated by congruence in the control group but not in the ASD group. Within this study Dichter et al (2007) also employed a further task of congruence, matched closely to the eye gaze task but using arrow stimuli. In this task both groups modulated the cognitive control network in accordance with congruency. This suggests that in ASD it is particularly in reference to social stimuli that the brain functions differently.

2.3.3.6 Social cognition

Social cognition deficits in ASD are most frequently discussed in terms of a mentalizing deficit or Theory of Mind dysfunction. The theory states that individuals with ASD have difficulty attributing the appropriate mental state to others and this may stem from difficulties in processing social information and cues from others. These cues may be in the form of facial expression but also extend to body posture, tone of voice and the more general context of the situation. In the investigation of irony comprehension, Wang et al (2006) studied the processing of social cues from voice stimuli. This is of particular interest because of a) the bias in most previous studies to present stimuli in the visual domain and b) misunderstandings of the use of sarcasm and irony and a tendency to take language very literally is often reported by those with high function autism and Asperger Syndrome. Participants in this study listened to short scenarios and were then asked to indicate via button press if the speaker 'meant what they said'. In the first condition, cues

to aid this decision were provided by both event knowledge i.e. information provided within the scenario, and by the speakers tone. These two cues were also provided alone in scenarios in which the information provided failed to indicate the sincerity of the speaker or the speaker used a neutral tone. In all conditions, the ASD group showed an overactivation relative to the control group in regions associated with the processing of social stimuli; superior temporal sulcus region, inferior frontal gyrus and middle temporal gyrus. In a later study (Wang et al., 2007), irony was investigated using both auditory and visual stimuli. Participants were again asked to make judgments on sincerity but this time provided with a visual storyboard accompanied by auditory clips providing prosodic information. When participants initially carried out this task, the ASD group had significantly less activation in the superior temporal gyrus, cerebellum and medial prefrontal cortex. However, when explicitly instructed to attend to either facial expression or tone of voice, activation of medial prefrontal cortex was no longer different between groups. Further analysis revealed that whilst medial prefrontal cortex was recruited by the ASD group when explicitly asked to attend to social cues within the stimuli, the control group always recruited this region when completing the task. Furthermore, the control group showed increased activation in bilateral medial prefrontal cortex and temporal regions when ironic stimuli was contrasted with non-ironic stimuli; this effect was not observed in the ASD group.

Whilst this suggests that during more complex and real life activities such as irony comprehension brain responses are different in ASD, the evidence from more basic perceptual tasks of social cues cannot be overlooked. As outlined above, various studies have reported differences in brain activation in ASD in response to facial expressions and there is also evidence from the auditory domain; hypoactivation of the superior temporal sulcus region has been reported in ASD in response to vocal (speech and non-speech) sounds in contrast to energy matched environmental sounds (Gervais et al., 2004).

Nevertheless studies have been designed to try and isolate higher level social skills such as mentalizing. Baron-Cohen et al (1999) asked participants to make inferences on the mental state of others from eye stimuli and contrasted this with a task in which identical

visual stimuli were presented, but participants made gender discrimination decisions. In contrast to the studies of basic emotion processing, in this study much more complex feelings and intentions were being attributed e.g. concerned, unsympathetic. The ASD group demonstrated significantly greater activation than the control group of bilateral superior temporal gyri and a relative underactivation of left inferior frontal gyrus, amygdala and right insula.

Pinkham et al (2008) used whole face stimuli and limited their investigation to a single social judgment; trustworthiness. The ASD group had less activation in right amygdala and fusiform face area and left ventrolateral prefrontal cortex than the control group when this experimental condition was contrasted with fixation baseline. When making trustworthiness judgments was contrasted with the more constrained baseline of making judgments of age, the control group demonstrated a modulation of the social brain network; increased activation of amygdala, superior temporal sulcus region and ventrolateral prefrontal cortex when judging trustworthiness. This effect was not seen in the ASD group. However, as an ROI analysis was conducted any compensatory activation elsewhere in the brain in the ASD group may have been overlooked.

Mason et al (2008) investigated Theory of Mind processing by asking participants to read a short scenario followed by a comprehension question. Within the ToM condition the comprehension of the passage required participants to make inferences about the mental state of the characters within the story. Two further conditions were included; sentences involving emotional information and sentences with a purely physical content. When each condition was contrasted with fixation baseline, it emerged that whilst the control group recruited ToM regions (middle temporal gyrus, superior temporal gyrus) only in response to the condition requiring mentalistic inferences to be made, the ASD group activated these regions in response to each condition and to a greater extent in the ToM condition. Whilst the circuitry serving ToM function appear to be present in ASD, their recruitment and modulation in response to task demands appears to be abnormal. Unlike the studies of basic face and emotion processing which frequently reported a relative

hypoactivation in the ASD group, there appears to be a pattern of hyperactivation in the ASD group in these more demanding tasks of social cognition.

2.3.3.7 Imitation

A more recent explanation for the triad of impairments in autism (in addition to the psychological theories described in the previous chapter) has been suggested in relation to imitation and the mirror neuron system (MNS). The MNS comprises populations of neurons (identified in anterior parietal cortex and the inferior frontal gyrus in humans) which have been shown to activate to both the execution of a particular motor action and in response to observing that same motor act performed by another (Gallese et al., 1996). Imitation deficits are commonly reported in ASD which have implications for the development of language and social skills. Not only is imitation a precursor skill for verbal language acquisition and the development of play skills but more recently it has been suggested to feature in social cognition and the development of theory of mind (Kaplan and Iacoboni, 2006). For successful basic imitation and complex mentalising to take place, another's cognitive perspective must be assessed and re-represented following the observation of their actions. The MNS has thus been proposed as a system enabling emotion understanding via action representation. On a neural level it is thought that whilst the inferior frontal gyrus and parietal cortex code the observed action, in the case of socially relevant and emotional stimuli the limbic system is also recruited via the insula, allowing internally felt emotional significance (Iacoboni *et al.*, 2005, Schulte-Rüther *et al.*, 2007). By understanding and coding the function of others actions, intention can be attributed and an understanding of another's mental state can be achieved.

The functional organisation of this system in autism has been investigated directly in the case of basic motor imitation (Williams et al., 2006) and the imitation of emotional facial expressions (Dapretto et al., 2006). Williams et al (2006) reported differences between group activations in a variety of regions, including areas known to be associated with mirror neuron function; anterior parietal lobe and somatosensory cortex. In the second study, during the observation of emotional faces (with a fixation cross over the eye

region) behavioural eye tracking data revealed no significant differences between the ASD group and controls in terms of the time spent fixating on faces, including the eye region. Further to this, no differences in the activation of fusiform gyrus or amygdala were reported, however the ASD group had significantly less activity in right inferior frontal gyrus. When the imitation of emotional facial expressions was contrasted with resting baseline, the relative hypoactivation of inferior frontal gyrus was bilateral and the extended system proposed to be involved in emotion processing via the MNS was also less active than in the control group including insula and periamygdaloid regions. Greater activation in the ASD group was seen in left anterior parietal and right visual association areas (Dapretto et al., 2006). Together these studies provide emerging neurophysiological evidence for mirror neuron dysfunction in ASD.

2.4 Discussion

2.4.1 Limitation of literature review methods

The review of literature was limited to studies which applied functional MRI that excluded other techniques of functional imaging. Positron emission topography (PET) and single photon emission computer topography (SPECT) were relatively few in number therefore this review has focussed solely on studies applying fMRI.

The methodology applied in the analysis of fMRI data varied throughout the literature and it was not always possible to know the exact details of the contrast that was carried out which led to the reported results. Furthermore, whilst the statistical thresholds applied and/or the use of ROI approaches was generally justified within each study, these factors made it difficult to contrast findings between studies.

The first aim of this review was to characterise the ASD cohorts investigated in fMRI studies to evaluate how representative this group was compared to the ASD population as a whole. This has implications when findings from fMRI studies are extrapolated to make inferences about the neurophysiology underlying autism in general. The repeated use of the same study participants in several studies may have skewed findings. However the extracted demographic data goes some way to indicating biases in sample selection in

fMRI studies of autism. Finally, this systematic review of the literature will also be influenced by a negative publication bias.

2.4.2 ASD study participants

The ratio of male to female participants in the fMRI literature in ASD would appear to be unrepresentative of the ASD population as a whole. Commonly reported gender ratios in autism are 4:1 and in Asperger Syndrome are 8:1 (Fombonne, 2003, Newschaffer *et al.*, 2007). The ratio of male to female study participants in fMRI studies of 14:1 is therefore unrepresentative of the ASD population. This is likely to be driven by the relatively small sample sizes investigated within each study which means researchers opt to exclude female participants to reduce additional variation in their sample. With the increase of multi-centre imaging, the recruitment of larger samples that are more representative of the ASD population will hopefully be possible.

There is a general bias in the fMRI literature of autism towards imaging adults, although there are some studies which recruited adolescents and children. Whilst this is unsurprising given the demanding nature of participating in fMRI experiments, as a developmental disorder which manifests in early childhood studying younger cohorts and carrying out longitudinal studies is imperative if we are to gain an understanding of the aetiology of autism. Both behavioural and imaging data suggest that people with ASD develop alternative and compensatory processing styles and strategies which will likely confound findings in adult populations. Case studies have been published using younger children (Grelotti *et al.*, 2005) suggesting that with enough preparation and the careful design of simple experimental paradigms the imaging of younger cohorts may be possible.

Again, due to the demanding scanner environment it is not surprising that there is a bias in the fMRI literature to investigate high functioning individuals. However, when there are reports of as many as 80% of individuals with autism having a co-morbid learning disability it is clearly an area that requires attention. In addition to the practical difficulties of scanning an autistic group with additional learning disability, recruiting an

appropriate comparison group is also a challenge with no clear solution, even in behavioural studies. Due to the complex behavioural profile of autism which presents both enhanced ability in some aspects of cognition in addition to broad ranging impairments, IQ may not be the most appropriate measure with which to ability match people with autism to a comparison group. Perhaps more stringent matching based on education, socioeconomic status, physiological developmental age (when investigating children and adolescents) and gender would be sufficient if tasks are then designed on which the groups could be performance matched.

2.4.3 The influence of specific task demands

Not only the stimulus type but also the task demands seem to be important factors when designing tasks to elucidate brain function differences in ASD. Many apparent contradictions in fMRI data using tasks of a similar nature with comparable study populations can be accounted for by the specific task instructions given. Critchley et al (2000) report a significant group x task interaction suggesting that the ASD group and control group responded differently to whether the task required them to explicitly attend to the emotional content of face stimuli or not. Differences in fusiform gyrus activity in response to face processing has been reported when participants carried out a perceptual emotion match task, but not a more linguistic emotion label task even though both tasks employed the same stimuli (Piggot *et al.*, 2004, Wang *et al.*, 2004). Finally, when investigating the effect of face familiarity on brain activation in autism, an implicit task where the condition of familiarity did not have to be attended to for successful task completion failed to reveal any differences between groups (Pierce et al., 2004). However when the task employed required participants to discriminate on the basis of familiarity, fusiform hypoactivation was reported in the ASD group (Dalton et al., 2005).

2.4.4 Are there differential social deficits?

Differences in brain activation between ASD and control groups has been reported in a wide range of task types from reading comprehension and visual processing to emotion processing and theory of mind tasks. However, there are several examples in the literature of tasks which identify no between group differences in brain activation, yet

when social stimuli are incorporated into the task a deficit in the ASD group becomes evident. For instance, when investigating brain responses to congruence, hypoactivation in the ASD group was not found in the task employing arrow stimuli but was when face stimuli were used (Dichter and Belger, 2007). Similarly, when attention modulation was investigated, brain responses when house stimuli were used did not differ between the ASD group and the control group. However, the same task involving face stimuli revealed a hypoactivation in the ASD group (Bird et al., 2006). In the auditory domain this pattern has been repeated. No differences were reported in response to environmental sounds, however vocal sounds resulted in less activation in the ASD group relative to the control group (Gervais et al., 2004). Both tasks that investigated biological motion reported hypoactivation in response to biological motion in the ASD group that was either not present or far less extensive than in response to motion derived from a non-biological source (Freitag *et al.*, 2008, Herrington *et al.*, 2007).

This suggests that it is particularly in reference to social stimuli that the brain functions differently in ASD, which is unsurprising given the nature of the clinical phenotype. It may be that the incorporation of any social element adds an additional layer of complexity to these tasks and it is this additional difficulty that results in atypical neural responsiveness in ASD. Alternatively, it may be that the core deficit in autism is specific to the processing of social stimuli and this will subsequently impinge on the completion of any further task, regardless of complexity. However, it is difficult to resolve the above evidence for a specifically social dysfunction in autism with the body of evidence from perceptual and executive function tasks outlined in the results section. Perhaps a multideficit model of autism needs to be considered. There is evidence that there may be a basic level perceptual deficit in autism; a predisposition to feature based processing and a more visually based approach to complex cognitive tasks. Perhaps this confers a particular disadvantage to the acquisition and development of social skills and language.

2.4.5 *Is it a modulation problem?*

Another repeated finding in tasks of various types, using a range of stimuli, is that whilst between group contrasts fail to identify any differences between ASD and control samples, suggesting that the typical neural circuitry is recruited in both groups, subtle modulation of this activation in response to task demands or intensity of stimuli is observed in the control group but not in the ASD group. Whilst the appropriate brain network is crudely recruited, finer and more subtle control of activity in these brain regions is lacking.

In tasks of facial emotion processing where the intensity of stimuli modulated brain responses in the control group, this additional level of responsiveness to the stimuli was not observed in the ASD group (Ashwin *et al.*, 2007a, Deeley *et al.*, 2007). In another face processing task, this time of neutral stimuli, whilst there were no differences between groups in response to task stimuli the control group modulated brain activity in response to attention demands, an effect not seen the ASD group (Bird *et al.*, 2006). Dalton *et al.* (2005) reported a modulatory effect on the fusiform gyrus with regard to the familiarity of the face stimuli presented in the control group but this effect was not present in the ASD group. Motion has been shown to modulate facial emotion processing in controls but not participants with ASD (Pelphrey *et al.*, 2007). In both studies investigating congruence, similar circuitry was recruited by both the ASD and control groups in response to processing information from eye gaze. However whether eye gaze was congruent or not with the appearance of a target, modulated the activity in this system in the control group but not the ASD group (Dichter and Belger, 2007, Pelphrey *et al.*, 2005). A lack of modulation in ASD has also been reported in lexical tasks. Again, broadly the control and ASD participants were reported to recruit typical neural circuitry for the task but the control group modulated this in accordance with the type of word (Harris *et al.*, 2006) or sentence (Mason *et al.*, 2008) presented whereas the ASD group did not. During an imitation task, specific task conditions were found to affect the levels of activity in the MNS and amygdala in the control group and whilst these brain regions did activate in the ASD group the variability in response to conditions was not observed (Williams *et al.*, 2006). Also in tasks involving understanding the intentions of others,

whilst control group activation varied in relation to the judgement they were making (Pinkham et al., 2008) or the ironic content of stimuli (Wang et al., 2007), these features of the task failed to modulate brain activation in the ASD group.

2.4.6 A Region Of Interest approach

In addition to these two studies directly addressing the function of the MNS in autism it is worth noting that a recurring theme across the fMRI literature in autism is aberrant activity in a component of the MNS; the inferior frontal gyrus. In executive function tasks involving planning (Just et al., 2006), response inhibition (Kana et al., 2006), attention switching (Belmonte and Yurgelun-Todd, 2003) and working memory (Koshino *et al.*, 2005, Koshino *et al.*, 2008) activity in the inferior frontal gyrus of autistic participants was reported to be significantly less than that of controls. Perhaps more relevant to the Mirror Neuron theory of autism, inferior frontal gyrus activity has also been reported to be abnormal during a range of social tasks; basic face processing (Hadjikhani et al., 2007), emotion processing from face stimuli (Ogai et al., 2003), making inferences on mental states from eye stimuli (Baron-Cohen et al., 1999) and interpreting irony (Wang et al., 2006).

Although it cannot be assumed that it is the sub-set of neurons with MN properties within the inferior frontal gyrus which are responsible for the reported differences in activation, it does suggest that inferior frontal gyrus function is of great interest in autism. It may be that rather than designing tasks to try and isolate a cognitive function, designing a range of tasks to investigate the modulation of a specific brain region may be a useful approach and the inferior frontal gyrus would seem like a suitable candidate for further investigation in autism.

2.5 Conclusion

2.5.1 Conclusions drawn from the review

It is clear that for pragmatic reasons the majority of the ASD cohorts studied using fMRI are not entirely representative of the ASD population as a whole. Whilst findings from these samples still add a valuable contribution to the understanding of autistic

neurophysiology the interpretation of findings should be extrapolated with caution. Effort is therefore required to address the sample selection issues in this field. The progression of multicentre imaging will allow for larger samples to be investigated and careful design of simple tasks may allow the study of lower IQ and younger cohorts.

Task design in general, including the selection of baseline conditions, requires careful consideration as both task demands and features of stimuli appear to have differential effects in ASD. The broad range of tasks used to investigate ASD and which report atypical brain activation also require investigators to be aware that even when designing a task with a specific element of cognition of interest, assumptions made about other aspects of the task may not adhere to the same assumptions that could be made about a typical population. Finally, parametric designs may be particularly informative when studying this population as modulation of activation seems to be consistently reported to be aberrant in ASD.

2.5.2 Implications for future studies

It is clear that during the investigation of brain function in ASD there has been an emphasis on the processing of social stimuli, in particular faces. This is not surprising given that the primary deficit in ASD is within social communication which is mediated by such cues as eye gaze and facial expression. Despite this focus on face processing it is still unclear if there is a difference in the neural response of individuals with ASD when they process faces; there have been reports of relative hypoactivation of face specific areas but also studies reporting no differences between ASD and control groups.

It is also unclear if there are neural deficits specific to emotion processing in ASD and whilst studies have included emotional stimuli, tasks have often not been designed or analysed in such a way as to isolate the emotional component of stimuli.

Finally, it is also unknown whether or not there are differences in the neural response of individuals with ASD when processing other kinds of social stimuli as the investigation of these types of social cues have been far more limited. Further to this, when social cues

such as voice tone and movement have been investigated in ASD, it has been within complex social cognition tasks and often in tasks where social information is presented in several stimulus domains. The response to social cues, other than faces, has not been investigated in isolation.

Much like the behavioural studies investigating emotion processing discussed in the previous chapter, there is emerging evidence from the imaging literature to suggest that there may be a global emotion processing deficit in ASD. Again however, the bias towards investigating facial emotion and the diversity of experimental paradigms applied prevents any conclusions to be drawn. It therefore still remains unclear whether individuals with ASD have specific impairments in processing face stimuli or whether a global emotion processing deficit can account for the social impairments seen in the condition.

Chapter 3 - Behavioural Investigation of Emotion Processing in ASD

3.1 Introduction

As detailed within chapter 1, behavioural evidence exists to suggest that emotion processing is atypical in ASD which may relate to deficits in Theory of Mind skills and/or derive from an atypical style of processing driven by weak central coherence. Emotion recognition from face stimuli has been the most robustly investigated (Adolphs *et al.*, 2001, Celani *et al.*, 1999, Hobson *et al.*, 1988b, Howard *et al.*, 2000, Pelphrey *et al.*, 2002), however a limited number of studies also suggest that people with ASD have difficulty interpreting emotion from gesture (Hubert *et al.*, 2007, Moore *et al.*, 1997). Similarly, in the auditory modality, evidence is emerging that recognition of vocal emotion may be impaired in ASD (Hobson *et al.*, 1988a, Mazefsky and Oswald, 2007, Rutherford *et al.*, 2002). The small number, diverse cohorts and varied design of these studies have prevented conclusions to be drawn as to whether there is a global emotion processing deficit in ASD, rather than a specific dysfunction in the processing of faces. The imaging evidence reviewed in chapter 2 provides mixed evidence as to whether a face processing deficit regardless of emotional content exists in ASD and the imaging data in regard to facial emotion processing is even less conclusive. We therefore initially sought to carry out behavioural tasks to investigate the perception of emotion from a range of social signals in people with ASD. Using tasks of comparable format in the same study cohort, emotion recognition from face, body movement and voice stimuli were investigated. This allowed the investigation of emotion processing in ASD in both the visual and auditory modality using both static and dynamic stimuli.

Within the literature investigating face emotion processing in ASD there have been reports that there may be a differentially severe deficit in the recognition of fearful faces (Howard *et al.*, 2000, Pelphrey *et al.*, 2002). However, this fear specific deficit has not been consistently reported and deficits in processing other emotions have also been identified (Adolphs *et al.*, 2001, Celani *et al.*, 1999, Hobson *et al.*, 1988b). Furthermore, there is evidence to suggest that in addition to basic emotion recognition deficits, people with ASD have difficulties making more complex social judgements from face stimuli (Adolphs *et al.*, 2001, Baron-Cohen *et al.*, 2001a). We therefore asked participants to

identify a range of basic emotions and also extended our investigation into social cognition judgements as associated with facial stimuli.

The main hypothesis was that we would find a global rather than specific deficit in emotion processing in ASD. More specifically, we hypothesised that 1) the ASD group would show deficits in emotion processing across a range of stimulus types, 2) that these deficits would extend across a range of emotional states and 3) that participants with ASD would also show related impairments in making social judgements.

3.2 Methods

3.2.1 Recruitment of ASD participants

23 individuals with ASD were recruited from ‘Number 6’, a drop-in centre and service provider for adults with AS or HFA in Edinburgh and the Lothians (www.number6.org.uk), with close links to the regional ASD health service. The development of successful recruitment strategies are outlined in the appended document entitled ‘Research At Number 6’ which was written at the request of the Project Manager of Number 6 to serve as a reference for future research studies. Control participants were recruited from the general population.

3.2.2 Participant details

The ASD group had a mean age of 32.5 years (s.d. 10.9 years) and consisted of 16 males and 7 females. Participants were excluded from the ASD group if they had a diagnosed co-morbid psychiatric disorder. The control group was matched by age [mean age 32.4 years (s.d. 11.1 years)] and gender (17 male, 6 female) and consisted of typically developing volunteers who reported no personal or family history (first degree relative) of ASD or a major psychiatric disorder. All study volunteers provided informed consent and the study was approved by the Local Research Ethics Committee.

3.2.3 Test Procedures

3.2.3.1 Diagnostic measures of ASD

All members of the ASD group had previously received a diagnosis of an ASD through multidisciplinary assessment by clinical services in South-East Scotland. DSM-IV diagnostic categories were confirmed through a combination of case note review and clinical assessment by a specialist in the diagnosis of Autism Spectrum Disorders in adults (Dr Andrew Stanfield).

To further characterize the current level of autistic behaviour, ASD participants completed the Autism Diagnostic Observational Schedule (ADOS) (Lord et al., 2000) conducted by a trained interviewer (Ruth Philip) whose ratings were previously found to be reliable with two independent ADOS examiners. Autistic characteristics were also quantified using the self-completed Autism Quotient (AQ) (Baron-Cohen *et al.*, 2001b), Empathy Quotient (EQ) (Baron-Cohen and Wheelwright, 2004) and Systemising Quotient (SQ) (Baron-Cohen et al., 2003).

3.2.3.2 Background measures of cognitive ability

Verbal, performance and full-scale IQ scores were obtained using the Weschler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) and National Adult Reading Test (NART) (Nelson and Willison, 1991). The Benton Test of Facial Recognition (Benton et al., 1983) was employed to establish basic face processing ability. Participants are asked to select pictures from an array of six unfamiliar faces which match a target face according to identity. Pictures in the array may vary from the target in terms of lighting and orientation.

3.2.3.3 Emotion recognition

Emotion processing ability was investigated across three stimulus domains; faces, body movement and voices.

a) Face tasks

A range of tasks was employed to investigate facial emotion processing. The first task was the Ekman 60 Faces Test from the FEEST (Young et al., 2002) in which participants have to select (via mouse click) a textual label to describe the emotion expressed in a face presented to them on a computer monitor. The stimuli were selected from Ekman and Friesen's (1976) pictures of facial affect series (see figure 3.1a). Each face stimulus was presented for 5 seconds and participants had a choice of six emotion labels: 'happiness', 'sadness', 'anger', 'disgust', 'fear' and 'surprise'. Ten trials for each emotion were presented in random order and participants received no feedback on task performance. The second task was the Emotion Hexagon task from the FEEST (Young et al., 2002) which employs the same task structure but stimuli are computer-morphed to differ in the extent to which they express the emotion, thus providing a more sensitive measure of emotion labelling ability.

A further two tasks of facial emotion processing were developed, both using stimuli from the JACFEE series (Matsumoto and Ekman, 1988), (see figure 3.1b). In the first Face Emotion Label task, participants were again presented with a face on the computer monitor for 5 seconds. This time participants had only five textual labels to choose from as 'surprise' was omitted to allow a more direct comparison between tasks involving facial emotion and those involving emotion in voices and body movements, for which 'surprise' stimuli were not available. [It has previously been reported that when processing auditory emotional stimuli, 'surprise' does not have distinctive characteristics to allow recognition among controls (Murray and Arnott, 1993) and it was therefore not included in the Voice Emotion Label task.] There were seven trials for each emotion and the 35 stimuli were presented in random order. In this task, participants indicated their response to the examiner but were given no feedback on their response. The second task to employ the JACFEE stimuli was a Face Emotion Match task. Participants were

required to match the target stimuli to another picture of a face according to the emotional expression and indicate their response to the examiner. Again, they had a choice of five as 'surprise' was omitted and there were 7 trials for each emotion presented in random order on the computer monitor. This task was included as it has no verbal labeling component.

b) Body movement task

In the Body Movement Emotion Label task participants were required to select a text label from a choice of five ('happiness', 'sadness', 'anger', 'disgust' and 'fear') to describe the emotion expressed in a short movie clip and again indicate their response to the examiner. The movies ranged from 5 – 10 seconds and consisted of individual male and female actors depicting one of five emotions with whole-body movements. No facial emotion was visible (see figure 3.1c). Ten trials of each emotion were presented in random order and responses received no feedback. The whole-body movement stimuli depicting basic emotions in full light is part of a standardised stimulus set from Atkinson et al (2004).

c) Voice task

In the Voice Emotion Label task participants were required to select a text label from a choice of five ('happiness', 'sadness', 'anger', 'disgust' and 'fear') to describe the emotion in vocal stimuli, and indicate their response to the examiner. Calder Vocal Emotion stimuli were used which last 5 – 10 seconds and consist of male and female actors saying strings of numbers in an emotional tone (Calder et al., 2004). Ten trials of each emotion were presented in random order and responses received no feedback.

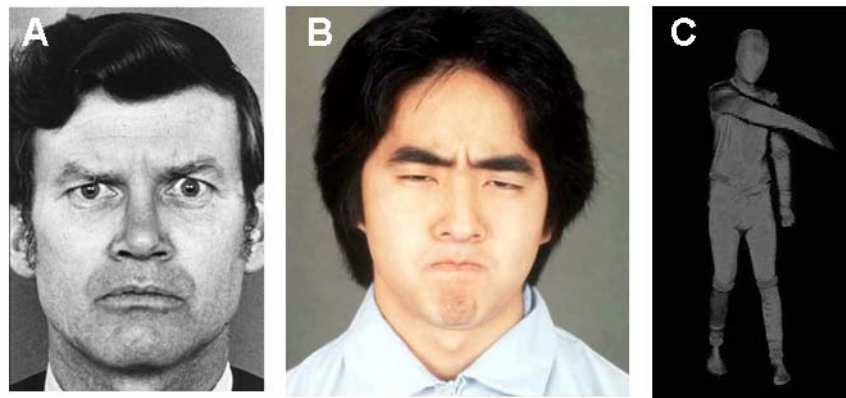


Figure 3.1 – Example stimuli from a) the Ekman 60 Faces Task and the Emotion Hexagon task, b) the Face Emotion Label task and Face Emotion Match task and c) a still taken from the Gesture Emotion Label task. All images depict the emotion ‘anger’.

3.2.3.4 Tests of Social Judgement (Social Cognition Test)

A final set of tasks tested participants’ ability to make a range of social judgements from faces (Hall *et al.*, 2004, Santos, 2003, Santos and Young, 2008). A database of one thousand pictures of faces of non-famous adults were derived from media sources and were rated by six volunteer participants on six social dimensions (age, trustworthiness, intelligence, attractiveness, approachability and distinctiveness) with 1 to 7 point scales for all characteristics. High inter-rater agreement was established using Cronbach's alpha coefficient, which demonstrated that the reliability of the ratings was high: 0.96 for age; 0.74 for distinctiveness; 0.89 for attractiveness; 0.79 for approachability; 0.75 for intelligence and 0.72 for trustworthiness. This indicated good agreement between the independent judgments of different raters (Santos, 2003). A mean rating was then computed for each facial stimulus on each characteristic and the selection of the stimuli for the social judgment tasks presented here was based on those mean ratings. For each dimension, 40 faces were selected comprising 20 faces representative of high and 20 faces of low valence to construct the final task. Each individual face appeared only in one set; completely different faces were selected for the sets of faces involving judgments of age, attractiveness, etc. The sets of faces for each social dimension were matched as closely as possible on the remaining five dimensions and half the stimuli were male and half female.

Participants in the present study were shown six sets of 40 faces (8 practice and 32 test images) on a computer monitor. Each stimulus was presented for 5 seconds. Participants were asked via text prompts to make a two-alternative forced-choice judgement on the face relating to age (old or young) in set 1, trustworthiness (very trustworthy or not trustworthy) in set 2, attractiveness (attractive or unattractive) in set 3, intelligence (very intelligent or not intelligent) in set 4, approachability (very approachable or not approachable) in set 5 and distinctiveness (very distinctive or not distinctive) in set 6. Responses were indicated to the examiner and again, no feedback was given to participants in relation to their responses. A response was considered an error whenever it did not correspond to the categorisation of the stimulus derived from the independent ratings. Therefore, if a face that had received a high rating on perceived intelligence, for example, was judged as unintelligent, this response was considered an error, (Hall *et al.*, 2004, Santos, 2003, Santos and Young, 2008).

3.2.4 Statistical analysis

Statistical analysis was carried out in Statistical Package for the Social Sciences (SPSS version 14 for Windows; SPSS Inc., Chicago, IL, USA). T-tests were used to investigate mean differences between the ASD and control groups in the AQ, EQ and SQ, measures of IQ and performance on the Benton Face Recognition Task.

Separate repeated measures Analyses of Variance (ANOVA) were employed for each task of emotion recognition and the social judgment task with emotion/judgment as the within-subject variable and group as the between subject factor. Following the investigation of effects of group, effects of emotion and group x emotion interactions, the effect of group was investigated for each emotion separately using independent t-tests. Standard residuals were examined to check that data was approximately normally distributed before parametric statistical tests were applied and unequal variance was taken into account in t-tests.

To illustrate the pattern of errors made by the control group and ASD group in the Face Emotion Label task, the Body Movement Emotion Label task and the Voice Emotion

Label task confusion matrices were constructed by calculating the number of times each emotion was given in response to a stimulus. By recording the responses given by participants when labeling emotional stimuli incorrectly this indicates which emotions participants confused. This then allows for the comparison of the types of errors made by each group.

As significant group differences were found in relation to IQ scores and performance of the Benton Face Recognition Test, the original analysis was repeated on subsets of the study population, matched on these measures. Exploratory analyses to test for group x gender interactions were also carried out for each emotion. Furthermore, due to the heterogeneity of the ASD sample, an exploratory analysis was carried out with the ASD group sub-divided according to diagnostic scoring.

Pearson's correlation was used to investigate associations between task performances across modalities in the emotion label tasks and the relationship between basic emotion label ability and social cognition.

3.3 Results

3.3.1 Diagnostic assessment

Within the ASD group 14 participants met DSM-IV criteria for AS, 7 for childhood autism and 3 for PDD-NOS. The ASD group scored significantly higher on each sub-set of the AQ compared to the control group ($p < 0.001$, see table 3.1) and significantly lower on the Empathising Quotient ($p < 0.001$). However there was no significant difference between groups on scores for the Systemising Quotient (see table 3.1). Despite the positive clinical diagnoses, only 11/23 participants scored above the ADOS cut-off for an ASD. Those who scored beneath the cut-off all had clinical diagnoses of either AS or PDD-NOS.

	ASD group mean(sd) (range)	Control group mean(sd) (range)	p-value
Autism Quotient (n=23, 23)			
Social skill	6.87 (2.62)	0.96 (1.19)	<0.001
Attention switching	8.26 (1.51)	3.65 (2.27)	<0.001
Attention to detail	6.70 (2.12)	4.83 (2.27)	0.006
Communication	6.70 (1.82)	1.74 (1.54)	<0.001
Imagination	5.87 (2.32)	1.96 (1.40)	<0.001
AQ total	34.39 (7.65) (21-46)	13.13 (5.46) (6-29)	<0.001
Scores > 26	19/23	1/19	
Empathy Quotient (n=20, 21)	33.45 (8.36) (21-52)	52.10 (15.44) (16-72)	<0.001
Systemising Quotient (n=18, 21)	27.61 (14.60) (4-66)	30.76 (12.97) (12-64)	0.484

Table 3.1 – Mean group scores with standard deviations and ranges for Autism, Empathy and Systemising Quotients. T-tests were applied to compare group means; p-values are displayed.

3.3.2 Background measures of cognitive abilities

Verbal and full scale IQ scores (VIQ and FSIQ) and IQ scores as estimated using the NART were lower in the ASD group than in the control group. Difference in performance IQ scores (PIQ) between the groups did not reach statistical significance (see table 3.2). For scores on the Benton Test of Facial Recognition the control group mean was 46 (s.d. 2.8), with a range of 41-52; all group members scoring in the non-impaired range. The mean ASD group score was 43.35 (s.d. 4.39), range 36-50. Whilst the mean score is within normal limits 4 members of the ASD group scored below 39 indicating a face recognition impairment (Benton et al., 1983). The difference between mean group scores was statistically significant, ($p=0.02$).

Test of IQ	ASD group mean(sd) (range)	Control group mean(sd) (range)	p-value
NART IQ	111.8 (7.6) (97-124)	115.9 (4.3) (108-124)	0.029
WASI VIQ	98.2 (15.8) (64-123)	106.8 (8.8) (86-120)	0.029
WASI PIQ	104.4 (18.6) (63-134)	113.4 (10.4) (96-129)	0.052
WASI FSIQ	101.5 (18.5) (60-126)	111.2 (8.5) (94-124)	0.029

Table 3.2 – Mean group scores with standard deviations and ranges for tests of IQ. T-tests were applied to compare group means; p-values are displayed.

3.3.3 Emotion recognition

3.3.3.1 Faces

Data for the 4 facial emotion tasks are presented in figure 3.2 and table 3.3. In the Ekman 60 Faces task there was a significant effect of group [$F(1,46)=27.7$, $p<0.001$], a significant effect of emotion [$F(5,230)=17.12$, $p<0.001$] and a significant group x emotion interaction [$F(5,230)=2.96$, $p=0.013$]. Post-hoc t-tests demonstrated that the ASD group performed significantly worse in the Ekman 60 Faces task across all six emotions ($p<0.05$), with the greatest impairment being apparent in ‘anger’.

In the Emotion Hexagon task, again there was a significant effect of group [$F(1,46)=17.46$, $p<0.001$], a significant effect of emotion [$F(5,230)=11.41$, $p<0.001$] and a significant group x emotion interaction [$F(5,230)=2.41$, $p=0.037$]. ASD group performance was poorer across all emotions in the Emotion Hexagon task. This reached statistical significance for ‘anger’, ‘sadness’, ‘fear’ and ‘surprise’ ($p<0.05$) with the greatest deficits seen in ‘anger’ and ‘fear’. Difference in performance in labelling ‘disgust’ reached trend level ($p=0.059$).

In the Face Emotion Label task (with ‘surprise’ omitted) the ASD group performed worse than the control group across all emotions. There was a significant effect of group [$F(1,46)=9.3$, $p=0.004$], a significant effect of emotion [$F(4,184)=10.69$, $p<0.001$] and a significant group x emotion interaction [$F(4,184)=3.17$, $p=0.015$]. The difference in group performance was then investigated for each emotion separately and found to be statistically significant for all emotions with the exception of ‘happiness’ and ‘fear’. In the Face Emotion Match task, there was a significant effect of group [$F(1,46)=10.1$, $p=0.003$], a significant effect of emotion [$F(4,184)=10.09$, $p<0.001$] and a significant group x emotion interaction [$F(4,184)=2.69$, $p=0.033$]. Group performance was similar between groups for ‘happiness’ but the ASD group scored lower on all other emotions. Again, statistically significant differences between the ASD and control group were found for all emotions with the exception of ‘happiness’ and ‘fear’.

Emotion Processing in Autism Spectrum Disorder

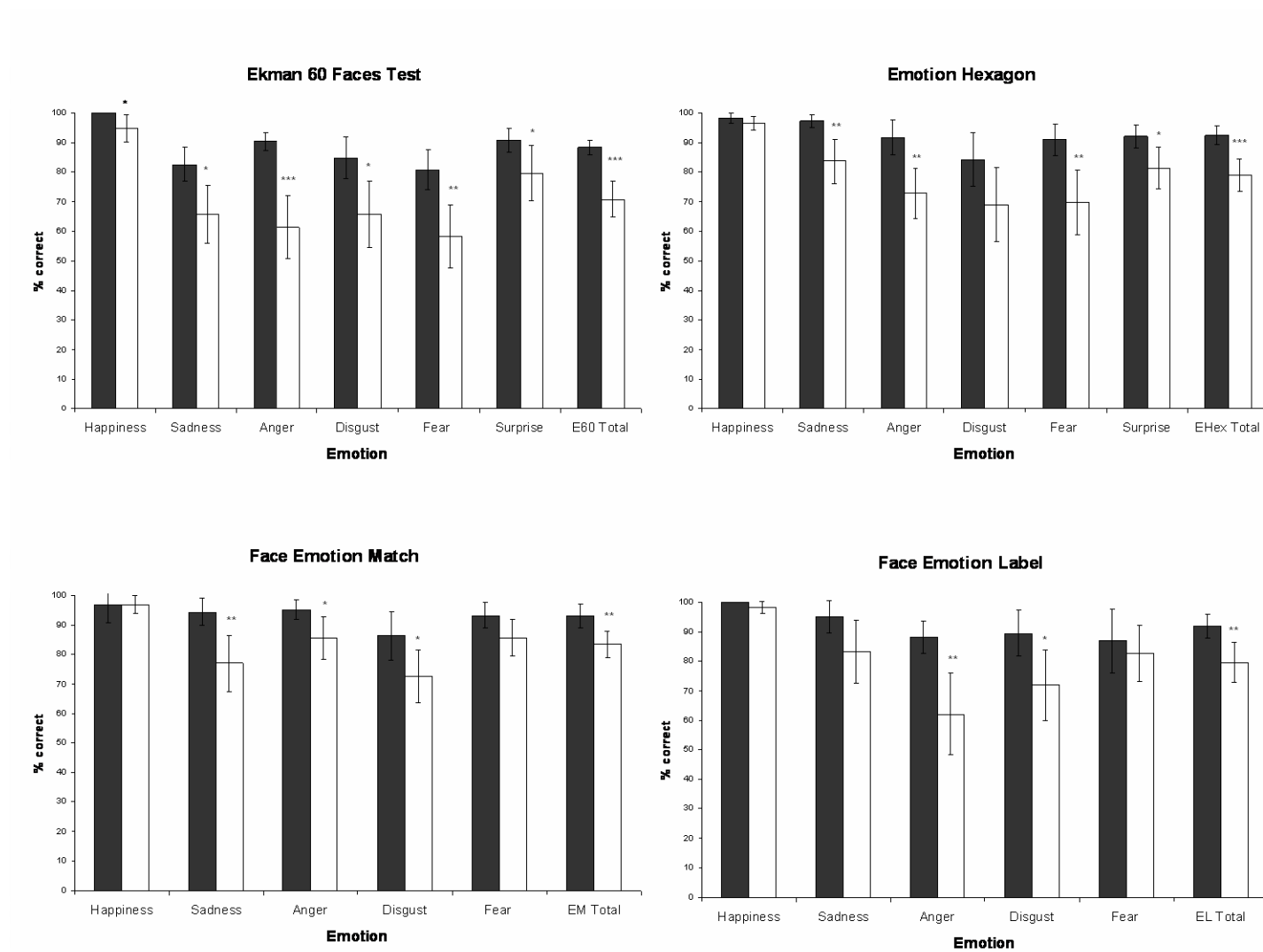


Figure 3.2 – Percentage of correct responses for each emotion in each facial emotion task; the Ekman 60 Faces task, the Emotion Hexagon task, the Face Emotion Match task and the Face Emotion Label task. Control group mean is in black, ASD group mean is in white. 95% confidence intervals are displayed. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

3.3.3.2 Body movement

There was a significant effect of group [$F(1,46)=17.42$, $p<0.001$) and a significant effect of emotion [$F(4,184)=18.82$, $p<0.001$) in the the Body Movement Label task, however there was no significant group x emotion interaction in [$F(4,184)=1.44$, $p=0.222$]. The ASD group was less accurate in identifying emotion from body movement for all emotions, with the greatest deficits being present in ‘happiness’ and ‘fear’. This difference was statistically significant ($p<0.05$) for all emotions except ‘sadness’ (see figure 3.3 and table 3.3).

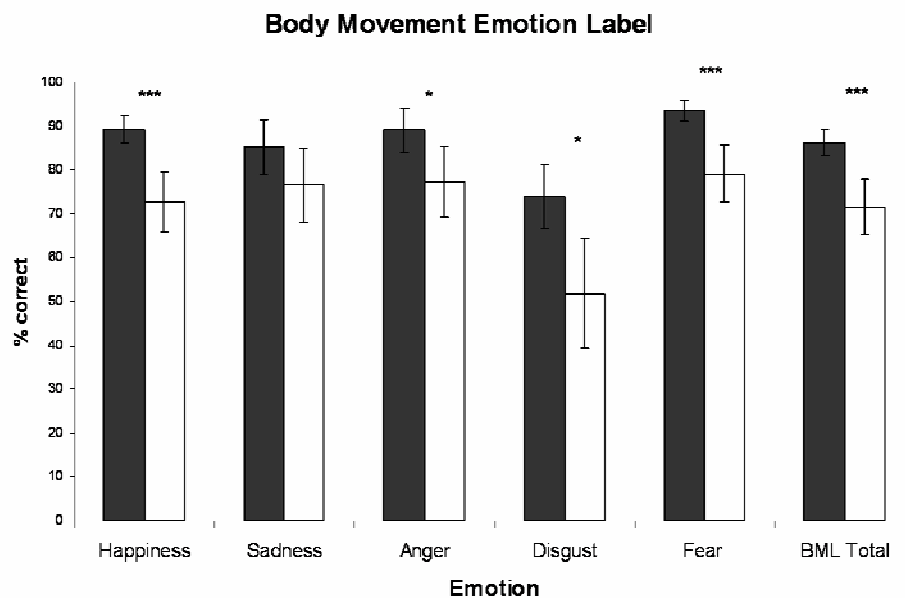


Figure 3.3 – Percentage of correct responses for each emotion in the Body Movement Emotion Label task. Control group mean is in black, ASD group mean is in white. 95% confidence intervals are displayed. * $p<0.05$, ** $p<0.005$, *** $p<0.001$.

3.3.3.3 Voices

In the Voice Emotion Label task, there was a significant effect of group [$F(1,46)=25.46$, $p<0.001$], a significant effect of emotion [$F(4,184)=5.53$, $p<0.001$] and a significant group x emotion interaction [$F(4,184)=2.89$, $p=0.024$]. The ASD group again scored lower than the control group across all five emotions, with the greatest deficits found in ‘anger’ and ‘disgust’. Differences in performance were statistically significant for all emotions ($p<0.05$ in all cases), with the exception of ‘sadness’ (see figure 3.4 and table 3.3).

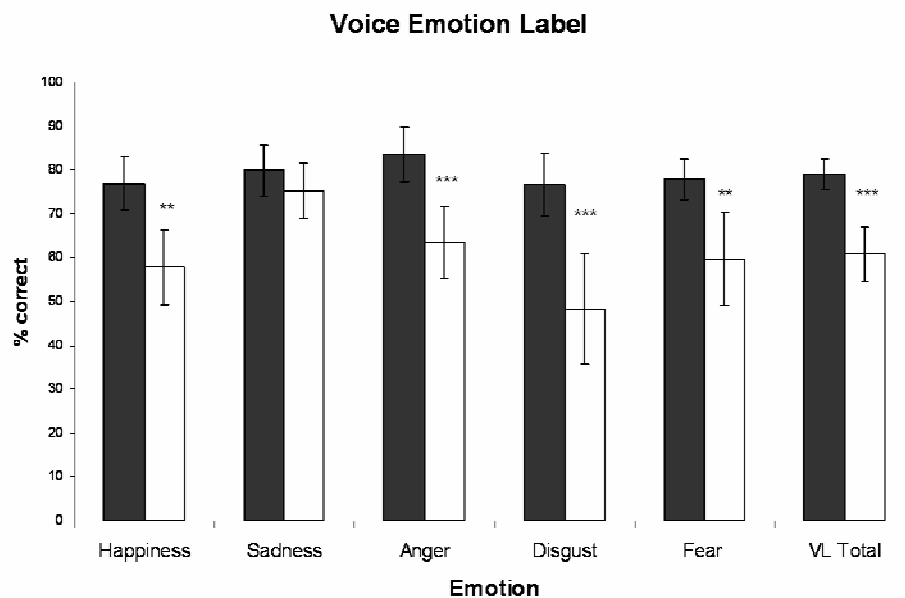


Figure 3.4 - Percentage of correct responses for each emotion in the Voice Emotion Label task. Control group mean is in black, ASD group mean is in white. 95% confidence intervals are displayed. * $p<0.05$, ** $p<0.005$, *** $p<0.001$.

Emotion Processing in Autism Spectrum Disorder

Ekman 60

Emotion	ASD group accuracy (%)	Sd	Control group accuracy (%)	Sd	p-value
Happiness	94.78	11.63	100	0	0.043
Sadness	65.65	24.09	82.61	14.21	0.006
Anger	61.3	25.99	90.43	7.06	<0.001
Disgust	65.65	27.44	84.78	17.29	0.007
Fear	58.26	26.05	80.87	16.49	0.001
Surprise	79.57	22.66	90.87	9.96	0.036
Total	70.74	14.79	88.3	5.47	<0.001

Ekman Hexagon

Emotion	ASD group accuracy (%)	Sd	Control group accuracy (%)	Sd	p-value
Happiness	96.52	5.73	98.26	4.16	0.246
Sadness	83.7	18.42	97.39	5.41	0.002
Anger	72.83	20.72	91.74	14.35	0.001
Disgust	68.91	30.82	84.35	22.27	0.059
Fear	69.78	26.44	91.09	12.88	0.001
Surprise	81.3	17.2	92.17	9.75	0.012
Total	79	13.67	92.43	7.57	<0.001

Face Emotion Match

Emotion	ASD group accuracy (%)	Sd	Control group accuracy (%)	Sd	p-value
Happiness	96.91	7.42	96.91	14.8	1
Sadness	77.04	23.16	94.43	11.2	0.003
Anger	85.65	17.84	95.09	8.15	0.028
Disgust	72.7	21.5	86.35	20.4	0.032
Fear	85.78	14.97	93.17	10.51	0.059
Total	83.61	10.87	93.09	9.48	0.003

Face Emotion Label

Emotion	ASD group accuracy (%)	Sd	Control group accuracy (%)	Sd	p-value
Happiness	98.17	4.82	100	0	0.083
Sadness	83.3	26.08	95.04	13.34	0.063
Anger	62.17	34.14	88.17	13.51	0.002
Disgust	72.09	29.39	89.48	18.85	0.022
Fear	82.65	23.12	86.96	26.25	0.558
Total	79.61	16.62	91.83	9.57	0.004

Body Movement Emotion Label

Emotion	ASD group accuracy (%)	Sd	Control group accuracy (%)	Sd	p-value
Happiness	72.61	16.85	89.13	7.93	<0.001
Sadness	76.52	20.8	85.22	15.34	0.114
Anger	77.39	19.82	89.13	12.4	0.021
Disgust	51.74	30.4	73.91	17.77	0.005
Fear	79.13	15.93	93.48	5.73	<0.001
Total	71.48	15.28	86.17	7.18	<0.001

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Voice Emotion Label

Emotion	ASD group accuracy (%)	Sd	Control group accuracy (%)	Sd	p-value
Happiness	57.83	20.66	76.96	14.6	0.001
Sadness	75.22	15.34	80	14.14	0.278
Anger	63.48	20.14	83.48	14.96	<0.001
Disgust	48.26	30.55	76.52	17.48	<0.001
Fear	59.57	25.85	77.83	11.66	0.004
Total	60.87	14.96	78.96	8.46	<0.001

Social Cognition Decision

Judgement	ASD group accuracy (%)	Sd	Control group accuracy (%)	Sd	p-value
Age	94.87	4.98	95.74	7.14	0.634
Trustworthiness	81.35	9.44	80.83	9.67	0.854
Intelligence	77.83	10.49	86.74	9.96	0.005
Approachability	79.61	16.6	93.13	6.19	0.001
Attractiveness	78.57	11.12	88.3	7.93	0.001
Distinctiveness	67.35	14.99	80.48	8.66	0.001

Table 3.3 – Task performance accuracy for all emotion and social tasks for the ASD and control groups. P-values for post hoc t-tests are also displayed.

3.3.4 Error patterns in basic emotion labelling tasks

The pattern of errors in each task for each group is illustrated in the confusion matrices (table 3.4). This data demonstrates that the number and type of errors made vary according to modality. The deficits in emotion labeling performance seen in the ASD group were a result of increased numbers of the same kind of errors made by the control group. In each task, whilst the ASD group made more errors than in the control group, the incorrect responses chosen reflected a similar pattern in both groups. From this it can be inferred that both groups are susceptible to the same types of errors, however the ASD group make significantly more of them.

3.3.5 Social Cognition

In the tasks of social cognition, there was a significant effect of group [$F(1,46)=17.48$, $p<0.001$], a significant effect of judgement [$F(5,230)=27.97$, $p<0.001$] and a significant group x judgement interaction [$F(5,230)=5.2$, $p<0.001$]. Further exploration with post-hoc t-tests identified no significant difference in performance between the ASD and control groups when making judgements on age and trustworthiness. However in judgements of attractiveness, intelligence, approachability and distinctiveness, the ASD group agree less well with standardised ratings than the control group. The difference in mean score for these attributes reached statistical significance ($p=0.001$ for attractiveness, approachability and distinctiveness, $p=0.005$ for intelligence) (figure 3.5 and table 3.3).

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Control Group Confusion Matrix for Face Emotion Label Task						ASD Group Confusion Matrix for Face Emotion Label Task					
Emotion	Response					Emotion	Response				
	Anger	Disgust	Fear	Happiness	Sadness		Anger	Disgust	Fear	Happiness	Sadness
Anger	0.85	0.12	0.01	0.00	0.02	Anger	0.65	0.25	0.04	0.00	0.06
Disgust	0.07	0.91	0.02	0.00	0.00	Disgust	0.16	0.73	0.06	0.02	0.03
Fear	0.01	0.12	0.87	0.00	0.01	Fear	0.03	0.09	0.84	0.01	0.03
Happiness	0.00	0.00	0.00	1.00	0.00	Happiness	0.00	0.02	0.00	0.98	0.00
Sadness	0.00	0.01	0.04	0.00	0.95	Sadness	0.01	0.08	0.05	0.01	0.85

Control Group Confusion Matrix for Body Movement Emotion Label Task						ASD Group Confusion Matrix for Body Movement Emotion Label Task					
Emotion	Response					Emotion	Response				
	Anger	Disgust	Fear	Happiness	Sadness		Anger	Disgust	Fear	Happiness	Sadness
Anger	0.90	0.08	0.00	0.01	0.01	Anger	0.77	0.15	0.02	0.03	0.04
Disgust	0.02	0.74	0.14	0.04	0.06	Disgust	0.09	0.51	0.17	0.03	0.20
Fear	0.00	0.05	0.93	0.00	0.01	Fear	0.04	0.06	0.81	0.02	0.07
Happiness	0.07	0.01	0.01	0.90	0.00	Happiness	0.20	0.04	0.01	0.74	0.00
Sadness	0.00	0.03	0.11	0.00	0.85	Sadness	0.03	0.04	0.18	0.00	0.75

Control Group Confusion Matrix for Voice Emotion Label Task						ASD Group Confusion Matrix for Voice Emotion Label Task					
Emotion	Response					Emotion	Response				
	Anger	Disgust	Fear	Happiness	Sadness		Anger	Disgust	Fear	Happiness	Sadness
Anger	0.83	0.08	0.00	0.07	0.01	Anger	0.59	0.22	0.04	0.11	0.04
Disgust	0.08	0.77	0.04	0.04	0.07	Disgust	0.12	0.46	0.12	0.14	0.16
Fear	0.01	0.03	0.80	0.08	0.09	Fear	0.05	0.07	0.58	0.18	0.12
Happiness	0.02	0.07	0.07	0.77	0.07	Happiness	0.02	0.11	0.16	0.56	0.16
Sadness	0.01	0.14	0.04	0.01	0.81	Sadness	0.02	0.08	0.09	0.05	0.76

Table 3.4 – Confusion matrices for the control and ASD groups for the Face, Body Movement and Voice Emotion Label tasks.

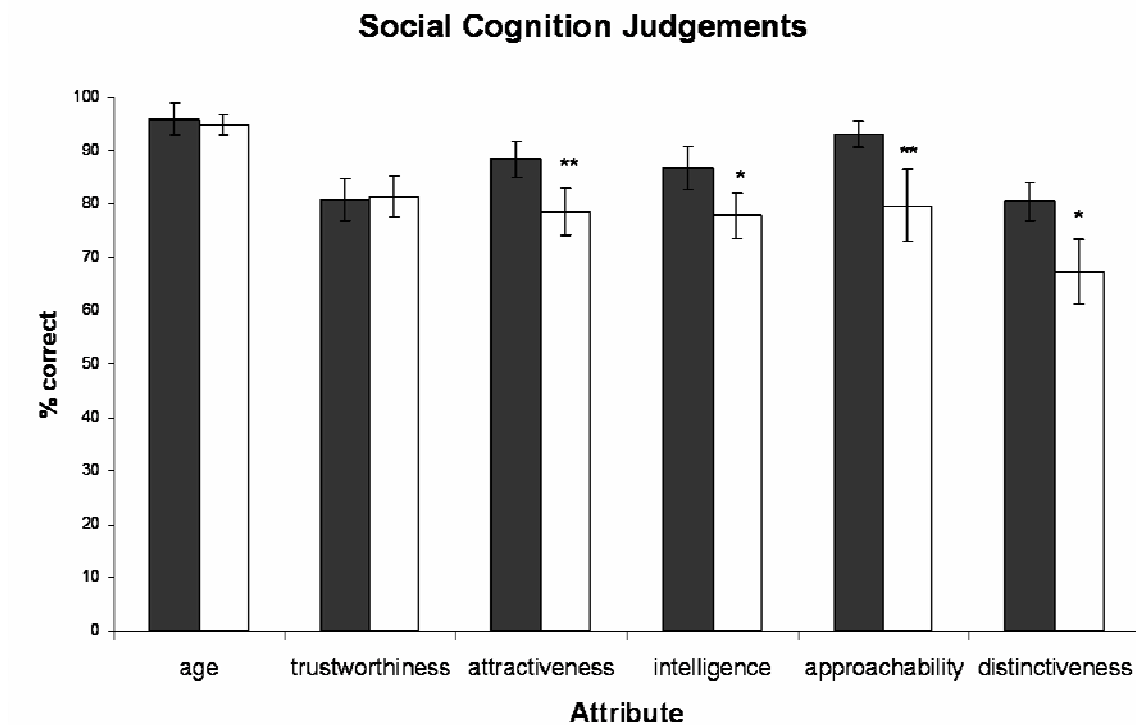


Figure 3.5 - Percentage of responses in agreement with standardised scores for each attribute in the task of social cognition. Control group mean is in black, ASD group mean is in white. 95% confidence intervals are displayed. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

3.3.6 Correlation of task performance across modalities and in relation to social cognition ability

As presented in figure 3.6, in the ASD group performance on each emotion labelling task was significantly and positively correlated with emotion labelling ability in the other two stimulus domains. Face Emotion Label performance correlated with Voice Emotion Label performance (Pearsons $r = 0.646$, $p = 0.001$) and Body Movement Emotion Label performance (Pearsons $r = 0.701$, $p < 0.001$). Voice Emotion Label performance also correlated with performance in the Body Movement Emotion Label task (Pearsons $r = 0.665$, $p = 0.001$).

The total emotion labelling score, an average score taken from each of the basic emotion label tasks, correlated with the average social cognition score in the ASD group (Pearsons $r = 0.48$, $p = 0.021$, figure 3.7). These correlations were not examined in the control group due to ceiling effects in task performance.

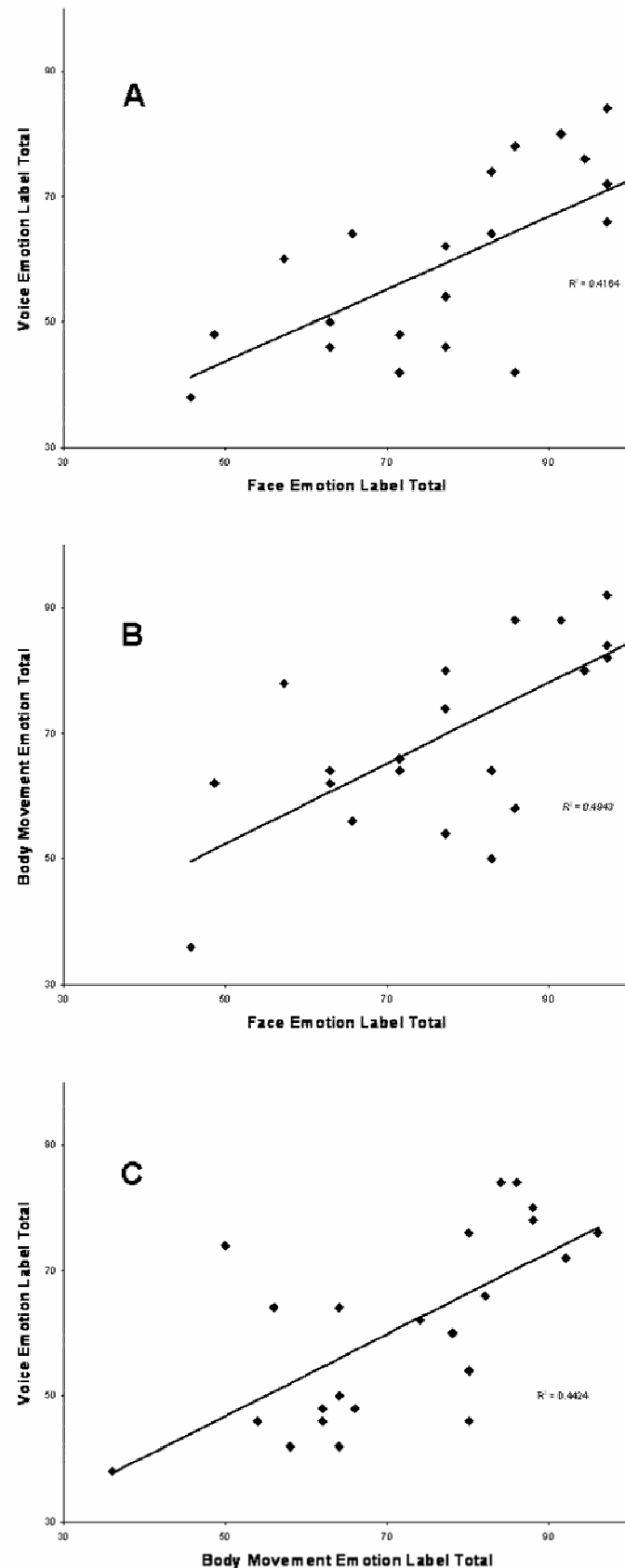


Figure 3.6 - Correlations between performance in each of the emotion label tasks in the ASD group. A) vocal emotion vs facial emotion B) body movement emotion vs facial emotion C) body movement emotion vs vocal emotion. All correlations are statistically significant ($p=0.001$).

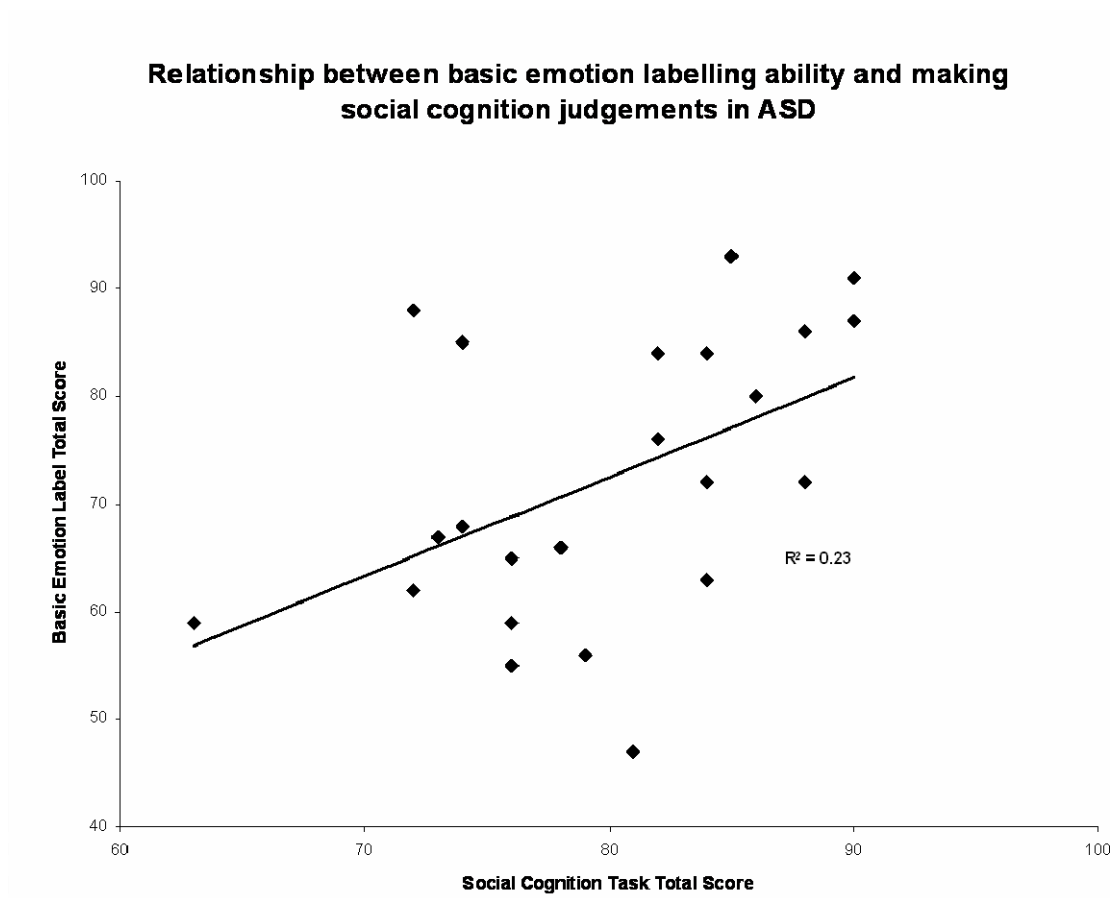


Figure 3.7 - Correlation between basic emotion labeling ability and performance in tasks of social cognition in the ASD group, ($p=0.021$).

3.3.7 Effects of possible confounds

The ASD group had a significantly lower full scale IQ (FSIQ) score than the control group ($p=0.029$) therefore a sub-set of participants ($n=17$ in each group) with matched IQ were selected and the original analysis repeated; repeated measures ANOVAs revealed a similar pattern of results to those seen in the full group (see table 3.5).

Similarly, as scores of the Benton Task of Face Recognition differed significantly between groups, ASD participants who had a Benton score indicative of face recognition impairment were excluded and the analysis of emotion and social tasks involving the face

stimuli were repeated. When groups were matched for Benton task performance, the original pattern of results remained, suggesting that deficits in face recognition do not account for the emotion processing impairments presented in this study (see table 3.6).

As the gender ratio in this ASD population (16:7) is somewhat higher than typically seen (4:1), the effect of gender was investigated; there was no significant gender x group interaction in any of the emotion or social cognition tasks.

An exploratory analysis was carried out to examine task performance with the ASD group sub-divided according to whether or not participants scored above diagnostic cut off on the ADOS (table 3.7). From this, it is evident that whilst there is a tendency for the ADOS positive group to perform more poorly than ADOS negative ASD participants, both groups show impairment relative to the control group. This is statistically significant for all tasks except the Face Emotion Label task where the difference between the ADOS negative group performance and controls only reached trend level ($p=0.097$).

Task	emotion*group		effect of emotion		effect of group	
	F	p	F	p	F	p
Ekman60	2.923	0.015	13.649	<0.001	14.194	0.001
Ekman Hexagon	2.064	0.073	7.666	<0.001	10.096	0.003
Face Emotion Match	1.823	0.128	7.832	<0.001	4.582	0.04
Face Emotion Label	2.079	0.087	9.231	<0.001	4.09	0.052
Voice Emotion Label	2.096	0.085	3.557	0.009	10.213	0.003
Body Movement Emotion Label	1.053	0.383	12.804	<0.001	10.469	0.003
Social Cognition Task	2.406	0.039	20.668	<0.001	11.15	0.002

Table 3.5 – Results of repeated measures ANOVA performed on subsets of the ASD and control groups. Control group; n=17, 12 male, age=29.7 (6.5), FSIQ=111 (9.1). ASD group; n=17, 12 male, age=33.5 (11.6), FSIQ=110.2 (11). T-tests revealed no significant differences between groups on age or FSIQ.

Task	Emotion*group		Effect of emotion		effect of group	
	F	p	F	p	F	p
Ekman60	8.14	0.007	12.66	0.001	20.38	<0.001
Ekman Hexagon	2.54	0.119	13.997	0.001	12.566	0.001
Face Emotion Match	13.176	0.001	17.768	<0.001	6.820	0.013
Face Emotion Label	6.858	0.012	14.612	<0.001	5.720	0.022
Social Cognition Task	31.194	<0.001	108.748	<0.001	15.359	<0.001

Table 3.6 – Results of repeated measures ANOVA with ASD participants with face recognition impairment excluded. Control group; n=23, 17 male, age=32.4 (11.1), Benton score=46 (2.8). ASD group; n=19, 15 male, age=33.2 (11.6), Benton score=44.7 (3.4). T-tests revealed no significant differences between groups on age or Benton score.

Emotion Processing in Autism Spectrum Disorder

Basic Emotion Processing Task Performance

Task	Control group accuracy (%)	Sd	ADOS –ve ASD group accuracy (%)	Sd	ADOS +ve ASD group accuracy (%)	Sd
Ekman60	88.30	5.47	73.83	14.56	67.36	14.98
Ekman Hexagon	92.43	7.57	81.33	13.53	76.45	14.00
Face Emotion Match	93.09	9.48	84.50	10.67	82.64	11.52
Face Emotion Label	91.83	9.57	84.00	17.67	74.82	14.70
Body Movement Emotion Label	86.17	7.18	72.67	18.32	70.18	11.88
Voice Emotion Label	78.96	8.46	62.83	16.72	58.73	13.24

Table 3.7 – Task performance accuracy (totals across all emotions) for all emotion processing tasks for the control group and the ASD group subdivided according to ADOS score. Control group; n=23, age=32.4 (11.1), ASQ=13.1 (5.4), FSIQ=111.2 (8.5). ADOS –ve ASD group; n=12, age=31.5 (11.2), ASQ=35.2 (7.8), FSIQ=105.3 (13.5). ADOS +ve ASD group; n=11, age=33.7 (11), ASQ=33.5 (7.7), FSIQ=97.4 (22.8). Bold indicates scores which differ significantly from controls following an independent t-test.

3.4 Discussion

3.4.1 Summary of results

We have demonstrated that people with ASD have significant impairments in emotion recognition across a range of stimulus domains *and* in the visual and auditory modalities. These results cannot be accounted for in terms of a failure to process emotional information in any single stimulus domain or sense modality and therefore strongly support the view that ASD involves a generalised impairment in emotion recognition. The same participants also had impairments in making other social judgements, suggesting that the deficits seen in emotion recognition could be part of a broader deficit in mental state attribution. Notably the deficits in emotion recognition correlated with the deficits in social judgement. The emotion and social processing impairments observed in the ASD group could not be accounted for by any differences in IQ or basic face processing ability between groups.

3.4.2 Cross modal deficits

The deficits displayed by the ASD group in each emotion processing task strongly support our hypothesis of cross-modal emotion processing deficits. Our findings of deficits in facial emotion processing across a range of tasks are in line with previous studies (Adolphs *et al.*, 2001, Celani *et al.*, 1999, Howard *et al.*, 2000, Pelphrey *et al.*, 2002). Using the Ekman 60 Faces task, we found a greater level of impairment than Pelphrey *et al.* (2002), which is likely to be due to the added power of our larger sample size. Previous reports [reviewed by (Sasson, 2006)] and indeed our own data from the Benton Task of Facial Recognition, suggest that basic face processing, regardless of emotion, may be deficient in ASD. However, differences were still apparent when the groups in the current study were matched for Benton task performance suggesting that the results are not purely accounted for by deficits in basic face processing.

Deficits in the task of emotion recognition from body movement replicate previous findings (Blake *et al.*, 2003, Hubert *et al.*, 2007) reinforcing the view that processing emotion from whole-body movement is also deficient in ASD. However the deficits in our ASD group appear less marked than those reported by Hubert *et al.* (2007). This

could be accounted for by the difference in demands in the body movement emotion label task applied here which used full body images as opposed to point light displays allowing a) full view of the body and b) low motion coherence requirements when depicting whole-body movement stimuli. Furthermore, in the Hubert et al study (2007) participants were asked to spontaneously generate descriptive language whereas our task provided a limited number of text options with which to respond.

We also demonstrated deficits in vocal emotion processing in the ASD group compared to the control group. This is in contrast to the findings of O'Connor et al (2007) who reported equivalent recognition of emotion from auditory stimuli in the ASD group relative to control group performance. This again may be accounted for by differences in the task design. Firstly, the task used in the current study provides participants with five options with which to respond; in the O'Connor et al study only three emotions were investigated. Secondly, in the O'Connor et al study, participants labelled auditory stimuli which they had already been exposed to in a previous emotion processing task which may have conferred an advantage. Our data indicates that deficits in emotion processing in autism also extend to the auditory modality.

Using comparable task formats in the same sample of individuals with ASD, deficits were present across three stimulus types which varied in presentation modality (visual and auditory) and presentation style (static and dynamic). Whilst the vast majority of previous emotion processing studies in ASD have utilised static facial representations of emotion (Adolphs *et al.*, 2001, Ashwin *et al.*, 2007a, Critchley *et al.*, 2000, Dalton *et al.*, 2005, Deeley *et al.*, 2007, Hall *et al.*, 2003, Howard *et al.*, 2000, Koshino *et al.*, 2008, Ogai *et al.*, 2003, Pelphrey *et al.*, 2002, Piggot *et al.*, 2004, Wang *et al.*, 2004) we show here that deficits in emotion recognition are not isolated to this type of stimulus. This broad ranging deficit in emotion recognition is therefore unlikely to be accounted for by processing demands or a processing style adopted for any specific stimulus domain. Differences in eye gaze pattern whilst processing static face stimuli (Dalton *et al.*, 2005, Klin *et al.*, 2002, Pelphrey *et al.*, 2002, Spezio *et al.*, 2007), for example, cannot account for the observed deficits in identifying emotion in body movement and voice stimuli.

Although we did not specifically monitor eye-gaze during our visual experiments the cross-modal impairments in the ASD group reported here, which include deficits in auditory emotion processing, could not be fully accounted for by atypical scan paths during face processing.

3.4.3 Cross-emotion deficits

Whilst previous studies (Howard *et al.*, 2000, Pelphrey *et al.*, 2002) demonstrated a differentially severe deficit in the identification of face stimuli expressing fear we report a deficit more broadly represented across basic emotions. We identified significant deficits in processing stimuli displaying ‘happiness’, ‘sadness’, ‘anger’, ‘disgust’ and ‘fear’ in support of our second hypothesis. That we found each of the basic emotions tested was impaired in at least one domain lends further weight to the idea of a global deficit in emotion processing in ASD. This suggests that impairments in emotion recognition in ASD lie in a substrate involved in the processing of a wide range of emotional states.

3.4.4 Social judgement deficits

The deficits in the ASD group extended to the tasks of social cognition in support of our third hypothesis. These tasks assess participants’ ability to make social judgements from a static facial image. Our finding of deficits in a range of decisions extends previous work which was limited to decisions relating to ‘trustworthiness’ and ‘approachability’ (Adolphs *et al.*, 2001). Whilst we replicated Adolphs *et al.* (2001) finding of differences in judging approachability, the ASD group studied here were equivalent to the control group in their judgements of trustworthiness. Differences in the format of the task used may account for this; Adolphs *et al.* (2001) provide a scale with which participants rate trustworthiness whereas in this study participants were asked to make a dichotomous decision. The overall poorer task performance in these social tasks however supports the notion of a generalised dysfunction in processing social information from human stimuli in autism as reported previously in studies assessing mentalizing ability (Baron-Cohen *et al.*, 1997, Baron-Cohen *et al.*, 1999, Castelli *et al.*, 2002, Frith, 2001, Happé *et al.*, 1996). The significant positive correlation between ASD participants’ performance of simple

emotion recognition and these social judgements provides evidence that basic emotion processing skills are predictive of more general social ability.

3.5 Conclusion

Within the same cohort of ASD participants, using tasks of comparable formats, emotion processing deficits have been identified across a range of stimulus modalities. This infers a global emotion processing deficit in ASD that cannot be accounted for by deficits in face processing alone. However, these behavioural findings fail to distinguish between two possible explanations for these findings: that there is a core emotion processing deficit in ASD which manifests itself in the processing of any type of emotional information regardless of stimulus type; or that there are basic processing deficits in both the visual and auditory domain that impinge on the processing of face, whole body and voice stimuli and confer further disadvantage when processing emotion from these social cues.

Chapter 4 - Functional Imaging

Investigation of Emotion Processing in ASD

4.1 Introduction

As outlined in chapter 3 the ASD cohort in the current study demonstrated deficits in processing identity from faces in addition to more severe difficulties identifying basic emotions from face stimuli. However, emotion labelling deficits were also identified in response to other stimulus types, including whole body images. Therefore within the neurophysiological investigation of this ASD sample, processing of both neutral and emotional stimuli were studied using both face and whole body representations of emotion.

4.1.1 Neural substrate of face and facial emotion processing in control populations

Functional imaging techniques have been applied to the investigation of face processing in typical populations since the early 1990s. One of the earliest studies by Sergent *et al* (1992) employed PET imaging and identified the right lingual and fusiform gyrus, the parahippocampal gyrus and the anterior temporal cortex as the network of brain regions required for face processing. Later fMRI studies have grossly replicated these findings, indicating bilateral fusiform gyrus activation along with other regions, including the superior temporal sulcus region (Ishai *et al.*, 2005, Posamentier and Abdi, 2003). A region within the fusiform gyrus of repeated peak activation across studies in response to faces has been identified and is referred to as the Fusiform Face Area (FFA). The FFA not only activates most strongly to the presentation of face stimuli, but also appears to be sensitive to the configuration and orientation of faces (Kanwisher, 2000). It is of note however, that it is as yet unclear whether the FFA is an innate region of face specialisation, or a region activated by stimuli for which experiential factors have led to a high level of expertise for that class of stimuli (Gauthier *et al.*, 2000, Tarr and Gauthier, 2000).

The evidence from a range of face processing tasks continues to implicate the same neural network as outlined above however specific task demands appear to differentially activate elements within this system. This has led to a model of face processing proposed by Haxby *et al* (2002) in which the inferior occipital gyri are suggested to be involved in early face perception i.e. the identification of facial features. The superior temporal

sulcus region is proposed to process changeable facial features such as eye gaze or expression. The intraparietal sulcus is suggested to be involved with managing information relating to directing attention. The fusiform gyrus is designated the role of identity recognition, with the anterior temporal cortex mediating the processing of biographical information, such as name. Within this network of brain regions, reciprocal and modulatory links are hypothesised. Further extensions to the system are also proposed, as information from faces is integrated with other neural networks. With each element of the neural system attributed its own specific function, the exact nature of the network recruited during face processing will likely depend on the specific task demands (Haxby et al., 2002).

Within this face processing network, the amygdala and insula are considered to be the brain regions involved with processing emotion from face stimuli. Not only does the processing of emotion from face stimuli affect how the above network is activated but there is evidence to suggest that slightly different regions are recruited depending on the emotion type presented. In the case of faces expressing fear, amygdala activation has been reported and this is generally found to be stronger in the left hemisphere. In addition, activity in the cingulate gyrus, insula and prefrontal cortex has been identified (Haxby et al., 2002).

4.1.2 Neural substrate of face and facial emotion processing in ASD

As discussed in detail in chapter 2, there has been a wealth of fMRI studies investigating the processing of faces in autism. In summary, there is evidence to both support (Dalton *et al.*, 2005, Pierce *et al.*, 2001, Schultz *et al.*, 2000) and refute (Bird *et al.*, 2006, Hadjikhani *et al.*, 2004a, Hadjikhani *et al.*, 2007, Kleinhans *et al.*, 2008, Koshino *et al.*, 2008) fusiform gyrus dysfunction in ASD during the processing of neutral faces. Further evidence exists to suggest that a more extended network of brain regions demonstrate aberrant activity during the processing of neutral faces in ASD compared to controls, including the superior temporal sulcus, premotor and somatosensory cortex, inferior frontal cortex and the amygdala (Bird *et al.*, 2006, Dalton *et al.*, 2005, Hadjikhani *et al.*, 2007).

There have also been many studies investigating the processing of emotional faces in ASD. Some have combined neutral and emotional face stimuli within one experimental condition, precluding the investigation of the component of emotion itself (Hubl *et al.*, 2003, Piggot *et al.*, 2004, Wang *et al.*, 2004). Others have designed paradigms to isolate the processing of emotional content. Dalton *et al* (2005) for example found no interaction between brain activation differences between the ASD and control group and the emotional content of stimuli. Several other studies have however reported differences in brain activation in ASD in response to facial emotion. In summary; Ashwin *et al* (2007a) reported a relative hypoactivation in the ASD group in the left amygdala and left orbitofrontal cortex in response to emotion; Deeley *et al* (2007) identified reduced activation of the bilateral fusiform gyrus, occipital and lingual cortex and cerebellum; Critchley *et al* (2000) also found reduced engagement of the fusiform cortex in addition to increased activity in the left superior temporal gyrus and peristriate visual cortex; finally Ogai *et al* (2003) reported reduced activity in response to fearful faces in the left middle frontal gyrus, and in the left insula, left inferior frontal gyrus and left putamen in response to faces expressing disgust.

However, within the study by Deeley *et al* (2007), the differences seen during emotion processing were also apparent when participants processed neutral faces. With the many reports of facial processing abnormalities regardless of additional emotional content it is difficult to determine if the aberrant activity seen in the autistic cohorts in response to emotion is merely an extension of face processing deficits or is representative of an independent source of emotion processing dysfunction.

4.1.3 Neural substrate of body and emotional body processing in control populations

Whilst the typical neural circuitry recruited to process faces and facial emotion is relatively well understood, there has been far less research into the brain activation seen in response to other social cues, for example body language. Biological motion is a dynamic visual display generated by the movement of a living organism, most often a person. The perception of biological motion has been investigated in typical populations

using functional imaging and is reported to involve a network of brain regions including the superior temporal sulcus region, the parietal cortex as well as regions of occipital and fusiform cortex and the amygdala (Bonda *et al.*, 1996, Grossman and Blake, 2002). Displays of dynamic body movement (including emotional gestures), in which more visual information than purely motion is provided, has been shown to induce activity in fusiform cortex and the amygdala (Grezes *et al.*, 2007).

Whilst the processing of dynamic body stimuli is of interest in terms of understanding how we process body language, the basic processing of static bodies is also important. Studies have reported a region of bilateral posterior inferior temporal cortex to reliably activate in response to whole body images; a region commonly referred to as the Extrastiate Body Area (EBA) (Peelen and Downing, 2005b). Additionally, a region of activation within the fusiform cortex in close proximity to the Fusiform Face Area has been shown to activate in response to body stimuli and so is named the Fusiform Body Area (FBA) (Peelen and Downing, 2005a). Whilst the FFA and FBA are known to be of close anatomical proximity, fMRI evidence supports the idea that these two regions of fusiform gyrus are selective for stimulus type (Schwarzlose *et al.*, 2005). Regions of the posterior superior temporal sulcus region have also been implicated in the processing of static body stimuli. Whilst this region is generally thought to be involved in the processing of dynamic stimuli, there is arguably an element of implied movement even within a static representation of a body (Peelen and Downing, 2007).

The neural mechanism underlying the processing of emotion from static images of the body in a control population has been examined by Hadjikhani and de Gelder (2003) and studied in combination with face processing by van de Riet *et al.* (2009). In the Hadjikhani and de Gelder study, participants were presented with static images of body stimuli in which the faces had been blurred. There were two conditions in this experiment: fearful and neutral. When the fear condition was contrasted with the neutral condition significant activation in bilateral fusiform gyrus and the right amygdala was seen. Van de Riet *et al.* employed an event related fMRI task with six conditions: fearful faces, happy faces, neutral faces, fearful bodies, happy bodies and neutral bodies. Again,

facial information was blurred in the body stimuli and all stimuli were static. Activity in the bilateral amygdala was increased in response to fearful stimuli relative to neutral stimuli whether the emotion was presented via faces or whole body images. The same effect was evident in the right superior temporal sulcus region.

4.1.4 Neural substrate of body and emotional body processing in ASD

Studying the response to whole body emotional stimuli presents a valuable opportunity to investigate emotion processing in ASD in addition to the face processing tasks generally applied. Investigating emotion processing from whole body stimuli avoids the possible confounds seen in face processing studies such as those associated with visual scan path differences and/or the aversion to eyes hypothesised to account for apparent differences in the ASD neural response (Dalton et al., 2005).

A small number of studies have recently been carried out to explore the processing of body stimuli in ASD. Two have been concerned with the processing of movement from social stimuli i.e. biological motion (Freitag *et al.*, 2008, Herrington *et al.*, 2007). Freitag et al (2008) reported that when biological motion stimuli were contrasted with scrambled versions of the same stimuli the control group activated a network of regions to a greater extent than the ASD group. This included the right middle temporal gyrus, medial and middle frontal gyrus, left anterior superior temporal gyrus and fusiform gyrus, and bilateral post central gyrus and inferior parietal lobule. Herrington et al (2007) contrasted biological motion with a fixation baseline condition and identified hypoactivation in the ASD group. Again an extensive network of brain regions were seen to activate differently in the ASD group including the bilateral cerebellum, fusiform gyrus, middle temporal gyrus, middle occipital gyrus and cuneus, right inferior temporal gyrus and inferior occipital gyrus, and left superior temporal gyrus, inferior parietal lobe, angular gyrus, precuneus and precentral gyrus. This evidence suggests that the neural response to social stimuli other than faces may be unusual in ASD.

Following on from their earlier work into emotional body processing in a control population, Hadjikhani et al (2009) have recently reported findings from the same fMRI

task applied to an ASD cohort. In a whole brain analysis, a between group contrast identified no significant differences between the ASD group and the control group when processing neutral static body images. However the authors report a network of hypoactivation in the ASD group when processing fearful stimuli including the visual cortex, amygdala, premotor cortex and inferior frontal cortex. In a further analysis, regions of interest for comparison between groups were selected based on the activation maps from the prior study in controls (Hadjikhani and de Gelder, 2003). The regions selected were the superior colliculus, pulvinar, amygdala, accumbens, putamen, fusiform gyrus, anterior insula, and the inferior frontal cortex. Within the fear condition, the control group activated each ROI investigated more than the ASD group. In the neutral condition, ASD hypoactivation was only observed in the inferior frontal cortex and the anterior insula. The between group contrast for the fear condition versus the neutral condition revealed differential activation in each of the ROI's investigated. Although the sample size in this study was small (ASD=9, control=7) the findings suggest that there may be a neural dysfunction in ASD that relates to the processing of social cues which is not limited or specific to face processing.

The available evidence therefore suggests that the neural response to social stimuli other than faces may be unusual in ASD. Further to this, by investigating emotion processing from two stimulus types in tandem, it may be possible to separate deficits associated with visual processing of a particular stimulus type from a broader dysfunction in emotion processing. In addition, the combined presentation of neutral and emotional stimuli within the same condition in previous studies has prevented the component of emotion from being isolated and examined in ASD. Even in the small number of studies where separate emotional and neutral conditions have been created, an analysis in which these conditions are directly contrasted has rarely been reported. The study of the neurophysiology underlying emotion processing deficits in ASD requires experiments that can address these issues and investigate 1) differences in the neural response to emotion independent of stimulus type and 2) differences in the neural response to the emotional component of social stimuli.

4.1.5 *The social brain*

Brothers (1990) defines social cognition as “the processing of information which culminates in the accurate perception of the dispositions and intentions of other individuals” and refers to autism as an example of “inborn selective absence of social cognition”. With this in mind and the evidence of broad ranging deficits in the processing of social cues presented in chapter 3, we need to consider not only the brain regions involved in face and body perception as described above but also the neural circuitry underpinning social cognition in general when considering the neuropathology of ASD. The neural network considered to be involved in social cognition is described below.

The circuitry thought to serve social cognition is collectively referred to as ‘the social brain’. Regions included in ‘the social brain’ are the superior temporal sulcus, orbitofrontal cortex and amygdala (Brothers, 1990). The amygdala has been shown to activate in response to face (Breiter *et al.*, 1996, Morris *et al.*, 1996), whole body (Grezes *et al.*, 2007, van de Riet *et al.*, 2009) and vocal (Fecteau *et al.*, 2007) representations of emotion, [see also review by Zald (2003)] and notably the amygdala has been implicated as dysfunctional in previous neuroimaging experiments in ASD (Ashwin *et al.*, 2007a, Baron-Cohen *et al.*, 1999, Critchley *et al.*, 2000, Dalton *et al.*, 2005, Wang *et al.*, 2004). It is important to consider however that the pattern of emotion processing deficits seen in autism is not equivalent to that of patients with amygdala lesions (Adolphs *et al.*, 2002, Sprengelmeyer *et al.*, 1999), suggesting amygdala dysfunction cannot fully account for the behavioural profile seen in autism.

The superior temporal sulcus (STS) region has similarly been implicated in theoretical models of emotion processing (Allison *et al.*, 2000, Calder and Young, 2005, Haxby *et al.*, 2002) and found to be functionally abnormal in imaging studies involving social paradigms in ASD (Boddaert *et al.*, 2003, Castelli *et al.*, 2002, Gervais *et al.*, 2004, Pelphrey *et al.*, 2005, Pelphrey *et al.*, 2007). Whilst originally proposed as a neural component serving changeable aspects of face processing it is now considered to be more broadly involved in social perception. In control populations the STS region has been

shown to activate in response to a broad range of social signals such as body movement (Grossman and Blake, 2002, Howard *et al.*, 1996), eye gaze (Hoffman and Haxby, 2000), mouth movement (Puce *et al.*, 1998), hand movement (Thompson *et al.*, 2007) and in response to human vocalisations (Belin *et al.*, 2000). This supports the idea raised by Calder and Young (2005) that the STS region is involved with the interpretation of any social signal with a temporal component. As well as activating in response to a variety of social cues, emotion expressed in facial (Simon *et al.*, 2006), whole body (Grezes *et al.*, 2007, van de Riet *et al.*, 2009) and vocal (Beaucousin *et al.*, 2007) stimuli have also been demonstrated to elicit activation in the STS region. This cross modal evidence implicates the STS region as an integrative system, processing social signals in terms of motion and emotion regardless of the stimulus modality or sensory domain. In autism, an STS region deficit has been identified from diverse stimulus types, from eye-gaze perception tasks (Pelphrey *et al.*, 2005) to the recognition of intentional movement from geometric shapes (Castelli *et al.*, 2002). This supports the STS region as a candidate locus for the neural substrate of the global emotion processing deficits reported in ASD.

Additionally, findings of more general deficits in social judgement in the ASD group not only implicate amygdala and STS region dysfunction (Adolphs *et al.*, 2006) but suggest broader deficits in the extended system required for social cognition. This includes orbitofrontal cortex, ventromedial prefrontal cortex and insula as outlined in models of the social cognition network (Adolphs, 1999, Allison *et al.*, 2000, Brothers, 1990, 1996).

4.1.6 Mirror neurons in social cognition

More recently the concept of the social brain has been extended further to include regions thought to contain mirror neurons which serve self-other action perception. These neurons activate when both the individual themselves carry out an action, or when they perceive another carrying out the same action (Rizzolatti and Fabbri-Destro, 2008). Regions found to activate in response to both action perception and execution have been found to lie in the dorsolateral prefrontal cortex, the precentral gyrus and the inferior parietal lobe. Whilst mostly investigated in terms of the perception and execution of

actions, evidence is also emerging to suggest that these neurons play a role during empathic interpersonal face-to-face interactions (Schulte-Rüther et al., 2007).

4.1.7 Outline of imaging study

To summarise, the behavioural findings in chapter 3 indicate a broad deficit in processing social stimuli in ASD. Data from the Benton Task of Facial Recognition supports the notion of a basic face processing deficit, consistent with previous literature. However, a face specific dysfunction cannot provide a full account for the deficits observed in terms of the cross modal nature of the emotion processing impairments.

An fMRI study was therefore designed in order to explore the neurophysiology that may underlie such deficits. Two fMRI tasks were carried out; the first employed neutral and emotional (fearful) faces and the second used static full body images depicting neutral and emotional (fearful) stances. This allowed for the study of the neural response to neutral examples of two types of social cues; faces and whole bodies. The inclusion of an emotional condition for each stimulus type permitted the investigation of the response to emotion depicted in different forms. Finally, by contrasting emotional and neutral examples of the same stimulus types, the element of emotion could be isolated. These tasks therefore allow the exploration of differences in brain function in ASD in relation to basic and emotional processing. By using two types of social stimuli, the question of whether the same neural substrate underlies the range of social deficits observed in ASD can begin to be addressed.

It was hypothesised that there will be differences between groups in the neural response to neutral face and body stimuli. Additional deficits in relation to the processing of emotional content in both modalities are also expected and may be more pronounced. It is predicted that the regions of aberrant activation in the ASD group will lie within the social brain network and that the neural substrate for deficits in emotion processing in both modalities will overlap, in support of a global emotion processing deficit in ASD.

4.2 Methods

4.2.1 Recruitment and participant selection

A subset of ASD participants from the behavioural study took part in the second stage of the study. During the first part of the study participants were informed that there would be a second part of the study which would include a scan and 21/23 were happy to be contacted again in relation to taking part. Participants were later approached to take part in the imaging study based primarily on matching demographic data between the ASD and control group and maximising the homogeneity of the sample. Only male participants were invited for a scan. All participants invited for a scan agreed to participate, reducing the possibility of a selection bias in the sample. Control participants were selected to match the ASD group as closely as possible on age, handedness and IQ. The inclusion/exclusion criteria for the imaging study were the same as for the behavioural study with the additional exclusion criteria of participants who contained ferromagnetic material; however no-one was excluded on this basis.

The ASD group consisted of 13 men with a mean age of 36.1 years (s.d. 11.8), 11 right handed, 2 left handed. One participant was excluded from the analysis due to excessive head movement. The control group was matched by age, gender and handedness and consisted of 12 healthy volunteers with no personal or family history of major psychiatric disorders. Demographic data is presented in table 4.1 in the results section. All study volunteers provided written informed consent and the study was approved by the Local Research Ethics Committee.

As outlined in chapter 3, all ASD participants had previously received a clinical diagnosis of an ASD. Of the 12 participants included in the image analysis, 8 had received a diagnosis of Asperger Syndrome and 4 a diagnosis of autism. 8 of these scored above the diagnostic cut off on the ADOS, however 4 of the participants, all with Asperger Syndrome, were sub-threshold on this diagnostic instrument.

4.2.2 Scan procedure

All usual procedures required by the Local Ethics Committee to ensure participants could provide fully informed consent were followed e.g. providing a study information sheet, providing time for participants to consider taking part and providing details of an independent contact that the study could be discussed with. In addition, as imaging a subject group with specific deficits in communication and particular anxiety over new situations, and potentially also some auditory hypersensitivity, further measures were taken to ensure that participants were prepared for the MRI scan. All details of the scan protocol were explained to participants (in some cases on several occasions) prior to the scan to ensure participants thoroughly understood what would be involved and they could provide fully informed consent to take part in the experiment. It was ensured that there were a variety of opportunities for participants to ask any questions and several members of staff at Number 6 were familiarised with the scan procedure or took part in an imaging experiment themselves so that they were also in a position to discuss any concerns participants may have had about taking part and the scanning experience. A short PowerPoint presentation on a laptop was used on the day of the scan to clearly outline, with visual supports, the order of events, the scan procedure, the tasks they would be asked to complete, and introduce the people they would meet. They were also played audio recordings of the scanner noise and could watch a video of someone undergoing a scan if they wished. Following this, all study participants completed a short practice task on a laptop which followed the same format as the tasks they would be asked to complete in the scanner and they used a hand paddle identical to that used in the scanner to make their responses.

Participants were scanned on a GE 1.5T Signa scanner at the SHEFC Brain Imaging Research Centre and the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh (www.sbirc.ed.ac.uk). Having signed written informed consent forms participants were checked for all metal objects and those who needed vision correction were fitted with scanner-compatible lenses. Participants were then taken into the magnet suite where they lay flat on the scanner bed. Headphones were provided to reduce exposure to scanner noise and allow the experimenter/radiographer to

talk to the participant in between scans. Foam padding was used to help minimize head movement and reduce scanner noise further. Participants were given a squeeze ball in their left hand and instructed to press this if they wanted the scan to stop. On their right hand the hand paddle was fitted so that they could respond to task instructions.

A T2 scan was obtained for clinical reporting. Six functional scans with identical parameters were acquired; 2 runs of the Faces task, 2 runs of the Body task and 2 runs of a social cognition task not reported on here. Functional scans comprised an initial localiser scan followed by echo planar image (EPI) sequence to acquire 99 volumes, TE 40ms, TR 2.5s. Interleaved axial slices were acquired AC-PC aligned with a thickness of 5mm with no gap and matrix size of 64 x 64. Tasks were presented using Integrated Functional Imaging Systems (IFIS) software (Psychology Software Tools Inc.). A T1 structural image was obtained; 180 slices were taken with a thickness of 1.2mm with no gap and matrix size of 192 x 192.

4.2.3 fMRI task design

4.2.3.1 Faces task

In this block-design task there were three conditions; fearful faces, neutral faces and baseline visual fixation (represented in figure 4.1). In the fearful and neutral faces condition, participants were shown the instruction 'Task' for 1s followed by 6 grey-scale faces (half male, half female with hair removed). Each stimulus was presented for 3.5s with an interstimulus interval of 500ms, making each block last a total of 25s. Stimuli in the fearful faces blocks had prototypical expressions of fear; in the neutral blocks stimuli were matched by identity to the fear block stimuli but had neutral expressions. Participants were asked to respond by pressing their right index finger each time a face appeared and were unaware that the emotional expression in the blocks would vary. Each block of faces were interspersed with the baseline condition where participants were asked to fixate on a white cross in the middle of a black screen. Blocks of visual fixation were 12.5s and preceded with the heading 'Rest'. There were 3 blocks of neutral and fearful faces and 8 blocks of visual fixation in total as each run began and ended with rest. Blocks of fearful and neutral faces alternated in order and whether the first block

was fearful or neutral was counterbalanced across study participants. There were two runs of the task, using two different sets of stimuli. Set 1 consisted of faces taken from Ekman and Friesen's Faces of Emotional Effect Series (Ekman and Friesen, 1976) and set 2 from the JACFEE/JACNEU series (Matsumoto and Ekman, 1988). Again, whether set 1 or set 2 was used in the first run was counterbalanced across study participants.

The task was preceded by a series of screens of instructions to ensure that participants were aware of which task they would be carrying out and remind them of the required response, again using visual support (see figure 4.1). The task was designed using E-Prime software and run using IFIS (Psychology Software Tools Inc.). Response time data were recorded for each participant whilst they completed the task in the scanner.

4.2.3.2 Body task

The design of this task was identical to the Faces Task but in place of facial stimuli, full body static images of fearful and neutral body expressions were used (Atkinson *et al.*, 2004, Atkinson *et al.*, 2007) (see figure 4.1). Whether participants completed the Faces task or Body task first was counterbalanced across groups.

4.2.4 Analysis

4.2.4.1 Demographics for groups

T-tests were applied to compare the ASD and control group in respect to age, full-scale IQ (Wechsler, 1999), the level of autistic traits as measured by the Autism Quotient (AQ) (Baron-Cohen *et al.*, 2001b) and basic face processing assessed using The Benton Task of Facial Recognition (Benton *et al.*, 1983). Response time was recorded during the fMRI tasks and this was also compared between groups using a t-test. All statistical analysis was carried out in Statistical Package for the Social Sciences (SPSS version 14 for Windows; SPSS Inc., Chicago, IL, USA).

4.2.4.2 Image analysis

Image analysis was carried out using Statistical Parametric Mapping (SPM) (Statistical Parametric Mapping, Institute of Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>). Data were reconstructed using standard techniques in SPM2 into ANALYZE format, using “dicom reconstruction”. Each reconstructed data set was then visually inspected for susceptibility artefacts. In addition, slice and volume anomalies were searched for using an automated procedure run by ArtRepair (Center for Interdisciplinary Brain Science Research, Stanford University, USA). Image preprocessing and analysis was conducted using SPM5 running in MATLAB (Version 6.5.1, The MathWorks, Natick, MA, USA). The first four volumes of each functional imaging run were discarded to avoid T1 equilibrium effects. During pre-processing, images were slice time corrected. Images were then spatially realigned to the mean EPI image using a 2 pass procedure to correct any small movements in head position during the scan. The graphical outputs of within-scanner movement data were examined for all participants; movement greater than 3mm in any axis across the duration of the scan (95 volumes) resulted in exclusion from any further analysis.

Data from each run was then coregistered with the mean realigned functional image. The T1 structural image for each participant was then segmented and functional and structural data normalised using the parameters generated from T1 segmentation. This ensured that functional and anatomical data for each study participant was in the same space and inferences could be made about the anatomical location of areas of significant changes in BOLD signal. Functional data were finally spatially smoothed using a Gaussian kernel (8mm^3 full-width at half-maximum) to minimise inter-subject differences and meet the assumptions required for statistical analysis. Images from all participants were inspected to exclude susceptibility artefacts.

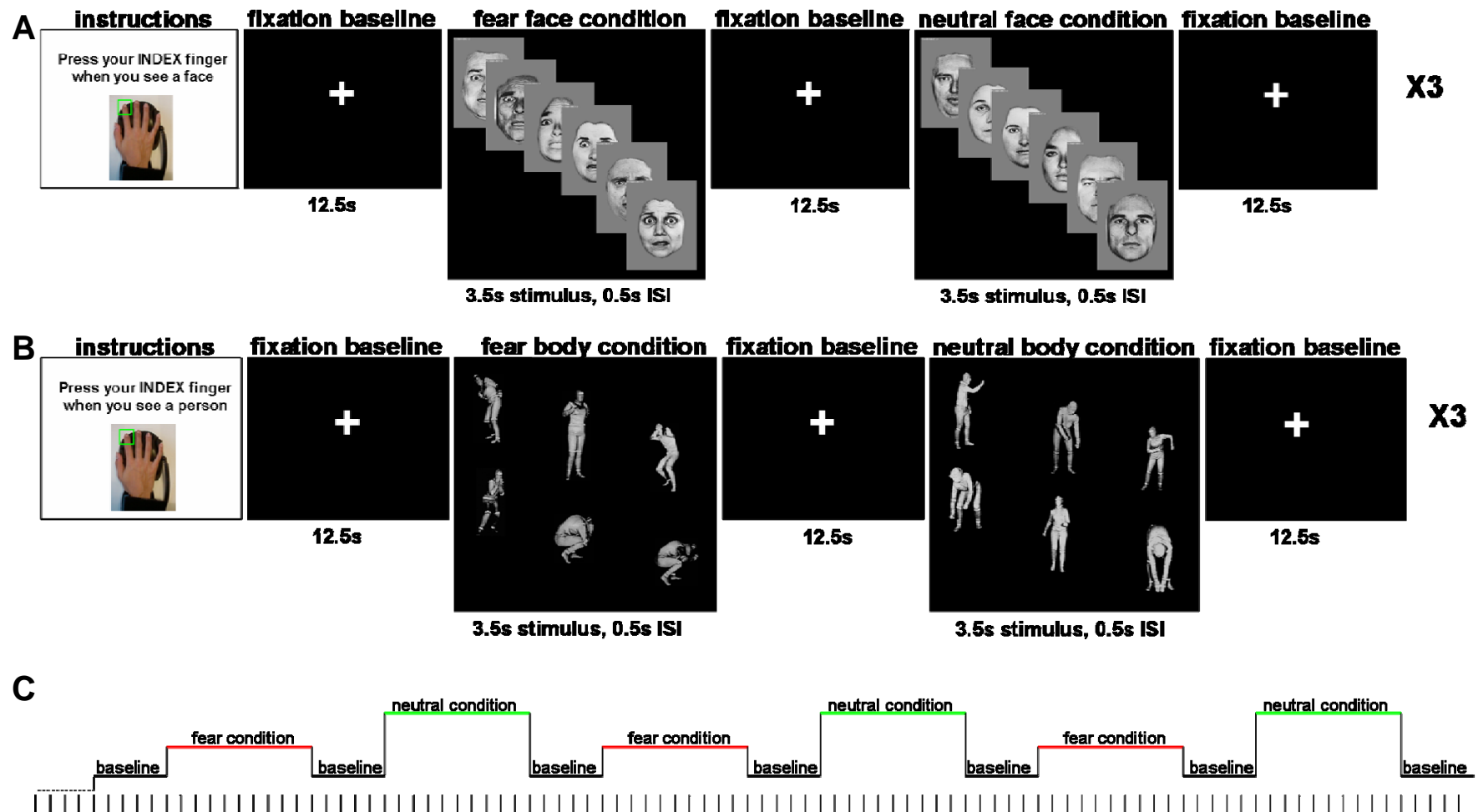


Figure 4.1 – Schematic of the first run of the face and body processing tasks. Run two was in an identical format but used different stimuli. A) Stimuli used in the face processing task. B) Stimuli used in the body processing task. C) Conditions presented in one run of the task, each point where BOLD signal was sampled (99 volumes in total) is represented by a vertical line.

Statistical analysis was performed using the general linear model in SPM5. A design matrix was generated to model the neutral and fear conditions for each task. Movement parameters for each participant were also entered as covariates of no interest into the design matrix (see figure 4.2). At a first-level analysis, contrast images were generated for each participant for the contrasts of interest for each task. These were 1) neutral condition vs baseline fixation, 2) fear condition vs baseline fixation and 3) fear condition vs neutral condition. These contrast images were then entered into a second-level analysis to examine regions of significant activation within each group (using a one sample t-test) and to investigate differences between the ASD and control group (using a two sample t-test).

A mask was applied to all maps to determine the voxels included in the analysis. Voxels were included within the mask if all values (over time and across all subjects) were non-zero and survived the initial F-test. Further to this, voxels were only included in the mask if values were above the threshold value. The default threshold is typically 0.8, however within the specific mask used in this analysis, this value was lowered to 0.3 in order to accommodate susceptibility variability between individuals in temporal lobe regions. This ensured that data from this region was included in the analysis. Within group statistical maps were thresholded at a level of $p=0.001$, corrected for multiple comparisons. Between group statistical maps were thresholded at a level of $p=0.005$, corrected for multiple comparisons.

4.2.4.3 Selection of contrasts of interest in the whole brain analysis

In both the face and body tasks the neutral condition was contrasted with baseline to investigate basic processing free from emotional content. Emotional (fear) blocks were contrasted with baseline in order to assess brain activation in response to emotional face and body stimuli. Finally, to isolate the component of emotion, blocks of fearful stimuli were contrasted with blocks of neutral stimuli.

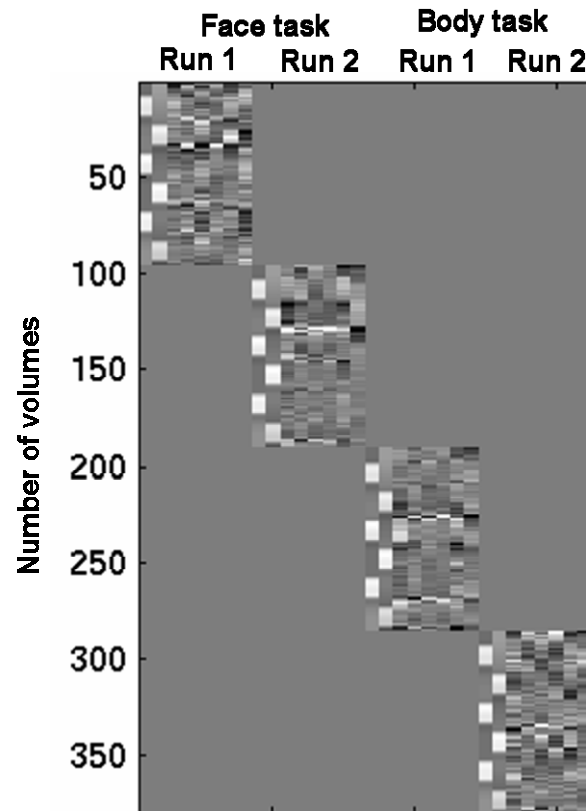


Figure 4.2 – An example of a design matrix used in the first level analysis. Within each run the first column represents the fear condition, the second the neutral condition and the final 6 columns contain the movement parameters for that participant.

As described above, two runs of each task were presented. However there is evidence to suggest that when processing emotional face stimuli, the neural response attenuates over time (Phillips et al., 2001). This was shown to be the case when the face task used here was employed previously in a separate study (Hall et al., 2008). Consequently, data from only the first run was used in the primary analysis. In order to maximise the comparability between the faces and body task the initial analysis was also limited to run1 in the body task. Subsequent analyses were performed on the body task, using data from both runs as there is no evidence to suggest that the neural response to body stimuli habituates over time as seen in faces.

4.2.4.4 Application of small volume corrections

Small volume corrections were applied to the whole brain analysis in regions where there were *a priori* hypothesis of group differences. The bilateral fusiform gyrus, superior

temporal lobe and the insula and amygdala are anatomical regions involved in face, body and emotion processing. Previous studies have reported aberrant activity in the fusiform (Dalton *et al.*, 2005, Pierce *et al.*, 2001, Schultz *et al.*, 2000), superior temporal gyrus and sulcal regions (Ashwin *et al.*, 2007a, Baron-Cohen *et al.*, 1999, Critchley *et al.*, 2000, Freitag *et al.*, 2008, Gervais *et al.*, 2004, Hadjikhani *et al.*, 2007, Herrington *et al.*, 2007, Pelphrey *et al.*, 2005, Pelphrey *et al.*, 2007, Pinkham *et al.*, 2008, Wang *et al.*, 2006, Wang *et al.*, 2008, Williams *et al.*, 2006), insula (Baron-Cohen *et al.*, 1999, Critchley *et al.*, 2000, Dapretto *et al.*, 2006, Dichter and Belger, 2007, Ogai *et al.*, 2003, Pelphrey *et al.*, 2005) and amygdala (Ashwin *et al.*, 2007a, Dalton *et al.*, 2005, Pelphrey *et al.*, 2007, Pinkham *et al.*, 2008, Williams *et al.*, 2006) in ASD samples in response to social cues. Regions were defined using the WFU Pickatlas toolbox (Advanced Neuroscience Imaging Research, Wake Forest University, USA) in SPM5 and during the second level analysis were applied as small volume corrections to the between group contrasts.

4.2.4.5 Conjunction analysis

To determine if there were regions of difference in common across the tasks overlay figures were created in SPM5 presenting group differences from the faces task alongside group differences from the body task. This was followed by a formal statistical comparison by way of a conjunction analysis in order to statistically test whether both tasks elicited significant aberrant activation in the ASD group in the same regions. A full factorial design was applied with two factors (group and stimulus type) with two levels for each factor (control and ASD; face and body). A between group contrast for fear vs baseline was carried out for each task and then these were entered into a conjunction analysis (see figure 4.3). This was thresholded at a level of $p=0.01$, corrected for multiple comparisons. (This reasonably liberal threshold was applied due to the relatively small group numbers.) The same process was repeated for the between group contrast of fear vs neutral for each task.

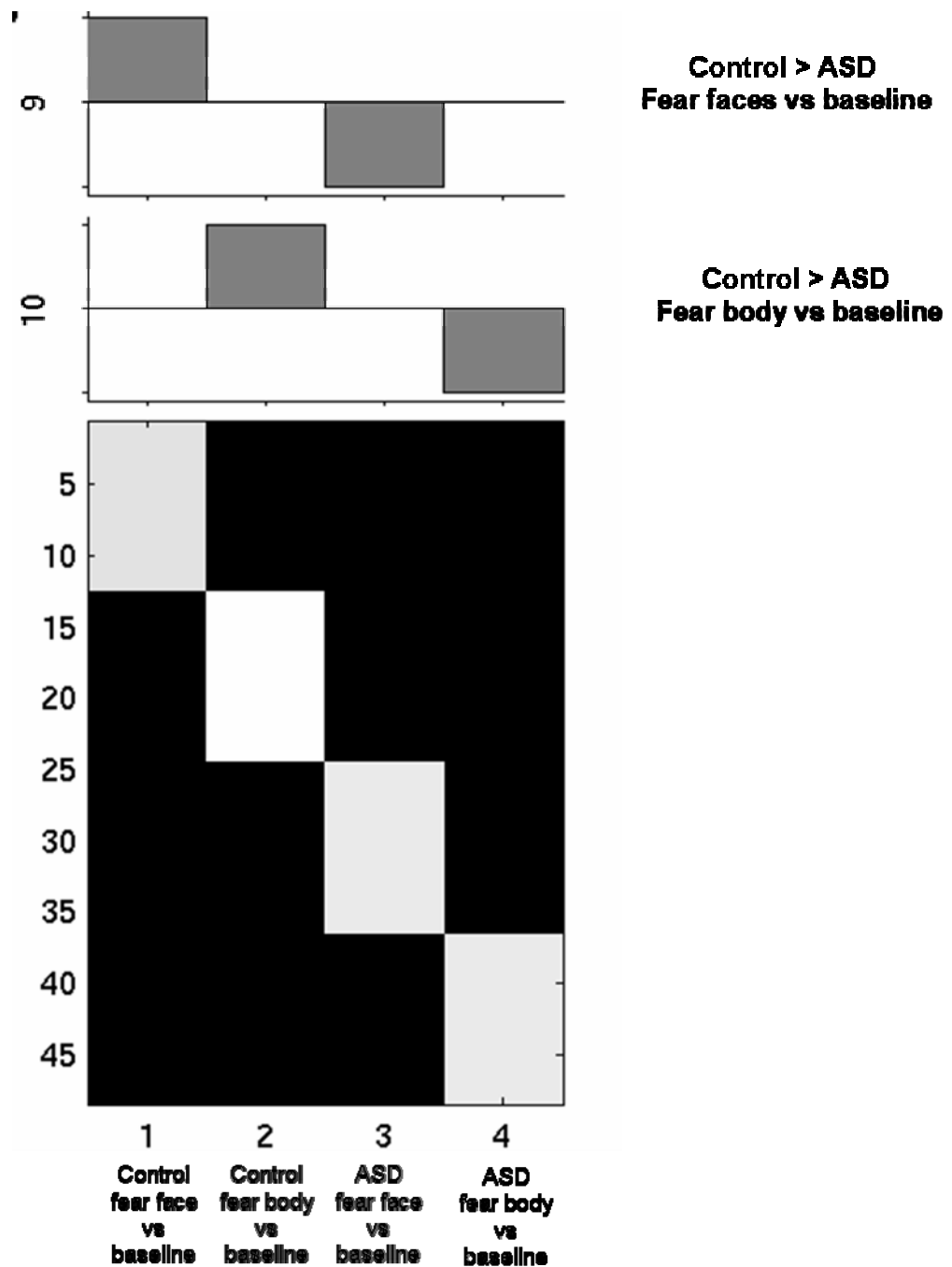


Figure 4.3 – The design matrix used in the conjunction analysis.

4.2.4.7 Effect of ADOS score

Four of the 12 participants in the ASD group did not reach the diagnostic cut off on the ADOS. In order to investigate whether these individuals were different in their neural responses than ADOS positive individuals, values were extracted from clusters of

significant group difference in the primary analysis. These were entered into SPSS where group differences were sought using Analysis of Variance followed by between group t-tests.

4.3 Results

4.3.1 Group demographics and behavioural performance

The control and ASD group were balanced group-wise on age, gender and handedness. There were also no significant differences between groups on FSIQ score. The ASD group had a significantly higher mean AQ score and lower mean EQ score as well as poorer performance on the Benton Test of Facial Recognition. There were no significant differences between groups on the within-scanner behavioural measures (table 4.1).

	ASD group mean(sd)	Control group mean(sd)	p-value
Age	35.4 (11.99)	35.09 (10.2)	0.945
Gender	12 M	12 M	
Handedness	9R, 3L	10R, 2L	
Autism Quotient	32.5 (7.45)	14.25 (3.77)	<0.001
Empathy Quotient (n=12, 11)	34.25 (8.33)	50.45 (11.44)	0.001
FSIQ	105.92 (19.83)	109.25 (10.48)	0.612
Benton score	44.25 (4.07)	47.25 (3.11)	0.055
RT during face task (ms)	871.9 (515)	801.7 (439)	0.723
RT during body task (ms)	826.1 (471)	827.09 (520)	0.996

Table 4.1 – Demographic data for groups included in the analysis of the face and body processing task. Additional relevant data is also included. Results of independent t-tests are displayed.

4.3.2 Imaging results

All participants successfully completed the scan procedure. One ASD participant was excluded from analysis due to excessive head movement, therefore n=12 for both the ASD and control group in subsequent results.

For each task three contrasts will be presented: 1) Neutral condition vs fixation baseline. 2) Fearful condition vs fixation baseline. 3) Fearful condition vs neutral condition. For each contrast, results of within group maps will be outlined, and between group

differences indicated when they were present. Following this, findings when small volume corrections were applied to the whole brain analysis will be described.

Additional analyses will then be presented. This will include a conjunction analysis where regions of common group difference in the face and body tasks will be explored. Finally, the neural response of ADOS positive and ADOS negative participants will be compared.

4.3.2.1 Basic processing of neutral social stimuli (Contrast 1)

Blocks of neutral faces were contrasted with fixation baseline to investigate the neural response to faces in each group. As detailed in table 4.2 and illustrated in figure 4.4, the control group mainly had peaks of activation in the bilateral fusiform gyri whilst the ASD group show a broader pattern of activation. Although there was a cluster of activity in the fusiform in the ASD group the activation peak of this large cluster was more inferior to that seen in the control group, located in the cerebellum. Whilst the network of brain regions recruited appear different between groups, when directly contrasted there were no significant differences in activation at the whole brain level.

When processing body stimuli, the control group recruited a more extensive network of brain regions than for processing face stimuli, which still included bilateral occipital cortex. The peak activation was in the right lingual gyrus. As in the faces task, there are no significant differences between the groups at the whole brain level, however as illustrated in table 4.3 and figure 4.5, the ASD group activate less extensively than the control group, and again the peak activation is displaced compared to the control group.

Contrast 1 - Neutral condition vs baseline - Faces

Region	Control			x	y	z
	cluster kE	Z score	cluster corrected p			
Right lingual/fusiform	2251	6.04	<0.001	20	-80	-12
Left fusiform	1443	4.88	<0.001	-34	-82	-16

Region	ASD			x	y	z
	cluster kE	Z score	cluster corrected p			
Right cerebellum	5018	5.75	<0.001	22	-48	-26
Left inferior parietal lobe	941	5.01	<0.001	-58	-26	46
Left hippocampus	353	4.79	<0.001	-30	-24	0
Left supplementary motor area	359	4.11	<0.001	-10	-2	56

Table 4.2 - Within group results for the control and ASD group when the neutral face condition is contrasted with visual fixation baseline. Only data from the first run of the task analysed. Threshold at 0.001, MNI coordinates displayed.

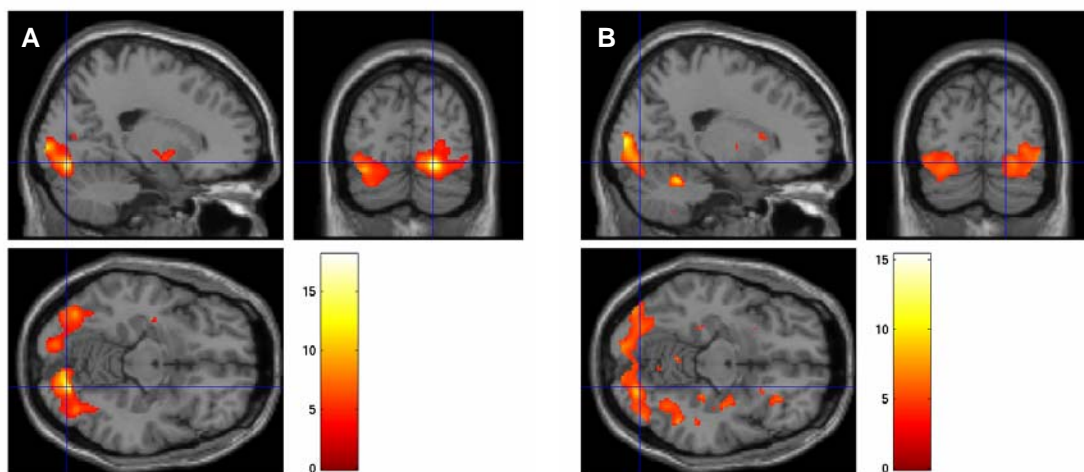


Figure 4.4A - Control fusiform activation in response to neutral face stimuli. B - ASD activity at the same coordinates.

Contrast 1 - Neutral condition vs baseline - Bodies

Control						
Region	cluster kE	Z score	cluster corrected p	x	y	z
Right lingual gyrus	7464	6.53	<0.001	10	-84	-10
Left precentral gyrus	1040	5.38	<0.001	-36	-12	62
Left hippocampus	219	4.56	0.003	-28	-32	-6
Right hippocampus	147	4.53	0.02	32	-10	-22
Left precentral gyrus	200	4.51	0.005	-56	4	30
Left supplementary motor area	443	4.26	<0.001	-14	10	68
Left insula	136	4.25	0.028	-24	24	2
Right rolandic operculum	200	3.83	0.005	44	-2	18
Left thalamus	234	3.83	0.002	-30	-2	6

ASD						
Region	cluster kE	Z score	cluster corrected p	x	y	z
Right inferior occipital lobe	2719	5.6	<0.001	42	-80	-2
Left middle occipital	1617	4.74	<0.001	-42	-82	-4
Left post central gyrus	180	3.8	0.038	-50	-20	54

Table 4.3 - Within group results for the control and ASD group when the neutral body condition is contrasted with visual fixation baseline. Only data from the first run of the task analysed. Threshold at 0.001, MNI coordinates displayed.

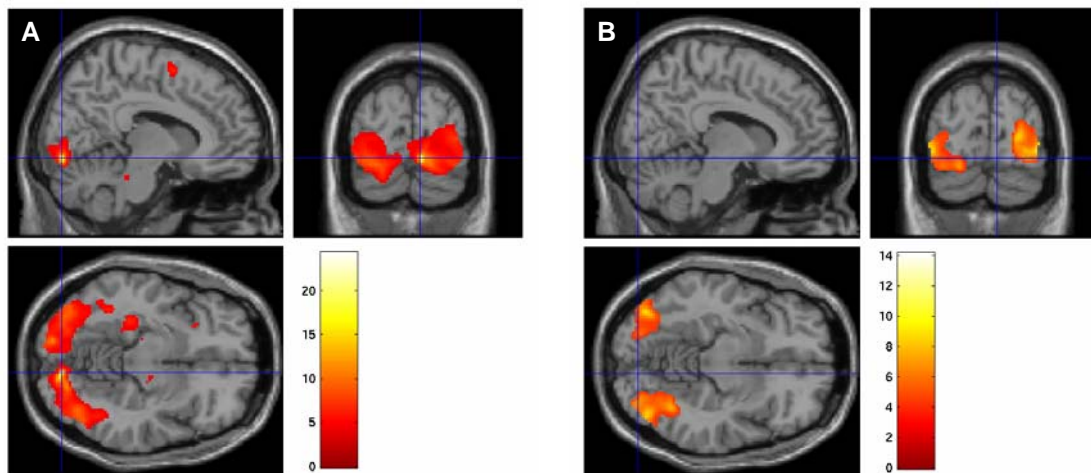


Figure 4.5A - Control fusiform activation in response to neutral body stimuli. B - ASD activity at the same coordinates.

4.3.2.2 Processing emotional stimuli (Contrast 2)

Blocks of fearful faces were contrasted with fixation baseline. Both the control group and the ASD group activated face processing regions; right fusiform gyrus and left lingual gyrus. Both groups also activated the right inferior frontal gyrus, part of the extended network involved in emotion processing. The control group significantly activate left insula and amygdala in response to fearful faces, which is not seen in the ASD group. The ASD group however, activate right middle occipital cortex and the left precentral gyrus. These differences in within group activation are illustrated in table 4.4 and figure 4.6, however a between group contrast revealed no significant differences in activation between groups at the whole brain level. There was a tendency for the control group to activate the left insula and right lingual gyrus more than the ASD group in response to fearful faces.

In the body task, the control group again activate the fusiform, as well as the pre- and post central gyrus, left superior temporal lobe and bilateral hippocampus. Activity in the ASD group is limited to bilateral occipital lobe (table 4.5 and figure 4.7). A significant between group difference was found in the right lingual gyrus with the control group activating to a greater extent than the ASD group ($p=0.021$ corrected at the whole brain level).

Contrast 2 - Fear condition vs baseline - Faces

Control						
Region	cluster kE	Z score	cluster corrected p	x	y	z
Left lingual gyrus	1928	5.56	<0.001	-14	-92	-14
Right fusiform gyrus	2640	5.37	<0.001	16	-84	-14
Left insula	318	4.08	0.001	-40	-8	12
Right inferior frontal gyrus	236	3.77	0.005	48	40	26
Left amygdala	144	3.58	0.046	-20	-4	-16
ASD						
Region	cluster kE	Z score	Cluster corrected p	x	y	z
Right fusiform	950	5.24	<0.001	42	-40	-20
Right middle occipital	1098	4.97	<0.001	24	-90	8
Left lingual gyrus	1656	4.93	<0.001	-14	-90	-12
Left precentral gyrus	161	4.77	0.003	-26	-26	60
Right inferior frontal gyrus	190	4.2	0.001	56	28	20
Control > ASD						
Region	cluster kE	Z score	Cluster corrected p	x	y	z
Left insula	339	3.63	0.125	-40	-4	-2
Right lingual gyrus	312	3.15	0.163	22	-58	0

Table 4.4 - Within and between group results for the control and ASD group when the fearful face condition is contrasted with visual fixation baseline. Only data from the first run of the task analysed. Threshold at 0.001, MNI coordinates displayed.

Contrast 2 - Fear condition vs baseline - Faces

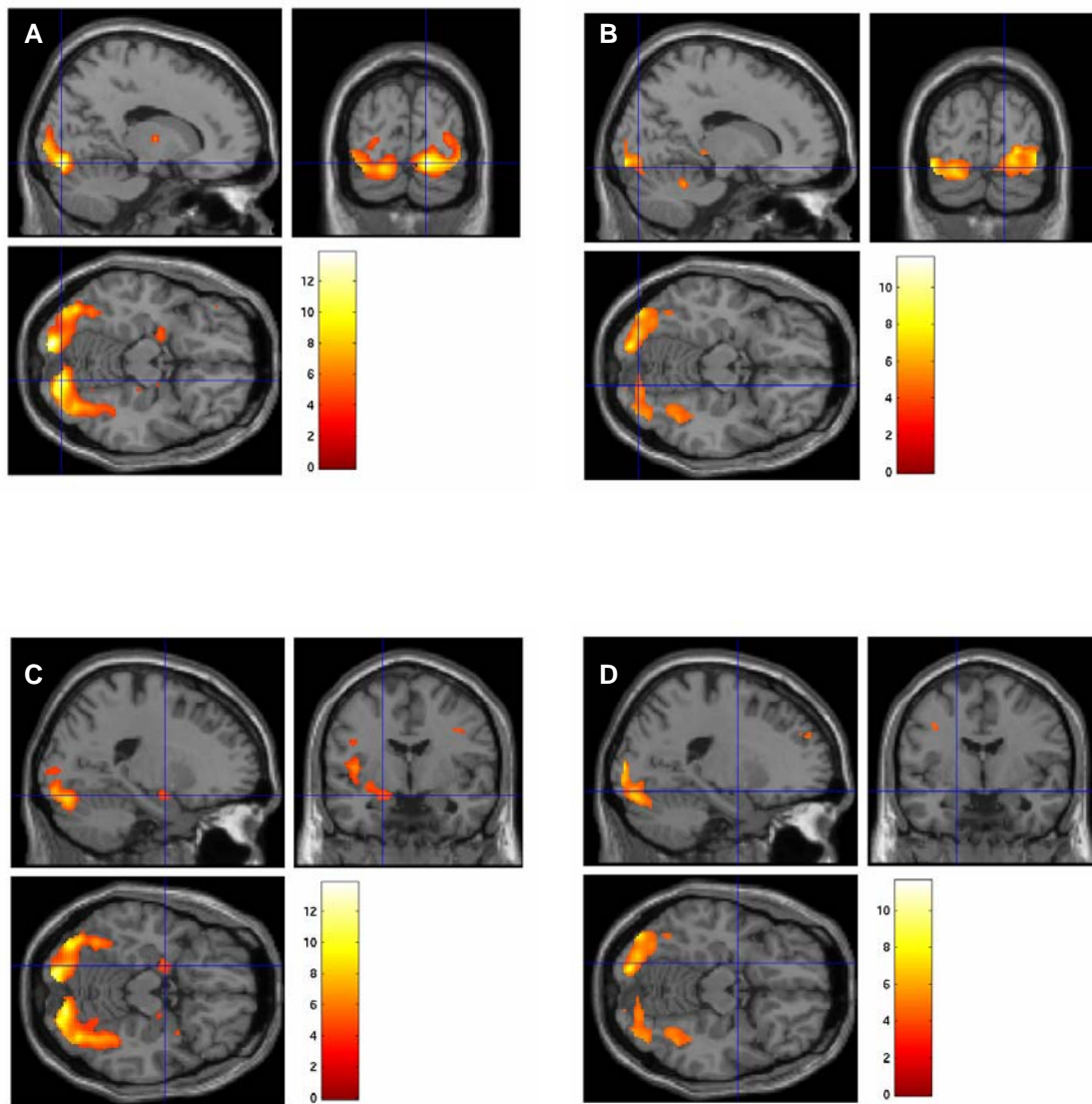


Figure 4.6A - Control fusiform activation in response to fearful face stimuli. B - ASD activity at the same coordinates as A. C – Left amygdala activation in the control group. D – ASD group map at the same coordinates as C.

Contrast 2 - Fear condition vs baseline - Bodies

Control						
Region	cluster kE	Z score	cluster corrected p	x	y	z
Right fusiform	7227	5.76	<0.001	18	-82	-14
Left precentral gyrus	1657	4.86	<0.001	-42	-8	60
Right postcentral gyrus	127	4.48	0.029	52	-26	44
Right precentral gyrus	145	4.38	0.016	60	6	30
Left superior temporal lobe	129	4.13	0.028	-56	-4	4
Left hippocampus	1196	4.05	<0.001	-18	-30	-6
Right hippocampus	177	3.95	0.006	16	-10	-16
ASD						
Region	cluster kE	Z score	Cluster corrected p	x	y	z
Right middle occipital	3539	5.93	<0.001	40	-76	2
Left inferior occipital	2087	5.34	<0.001	-44	-80	-4
Control > ASD						
Region	cluster kE	Z score	Cluster corrected p	x	y	z
Right lingual gyrus	567	3.85	0.021	12	-88	0

Table 4.5 - Within group results for the control and ASD group when the fearful body condition is contrasted with visual fixation baseline. Only data from the first run of the task analysed. Threshold at 0.001, MNI coordinates displayed.

Contrast 2 - Fear condition vs baseline - Bodies

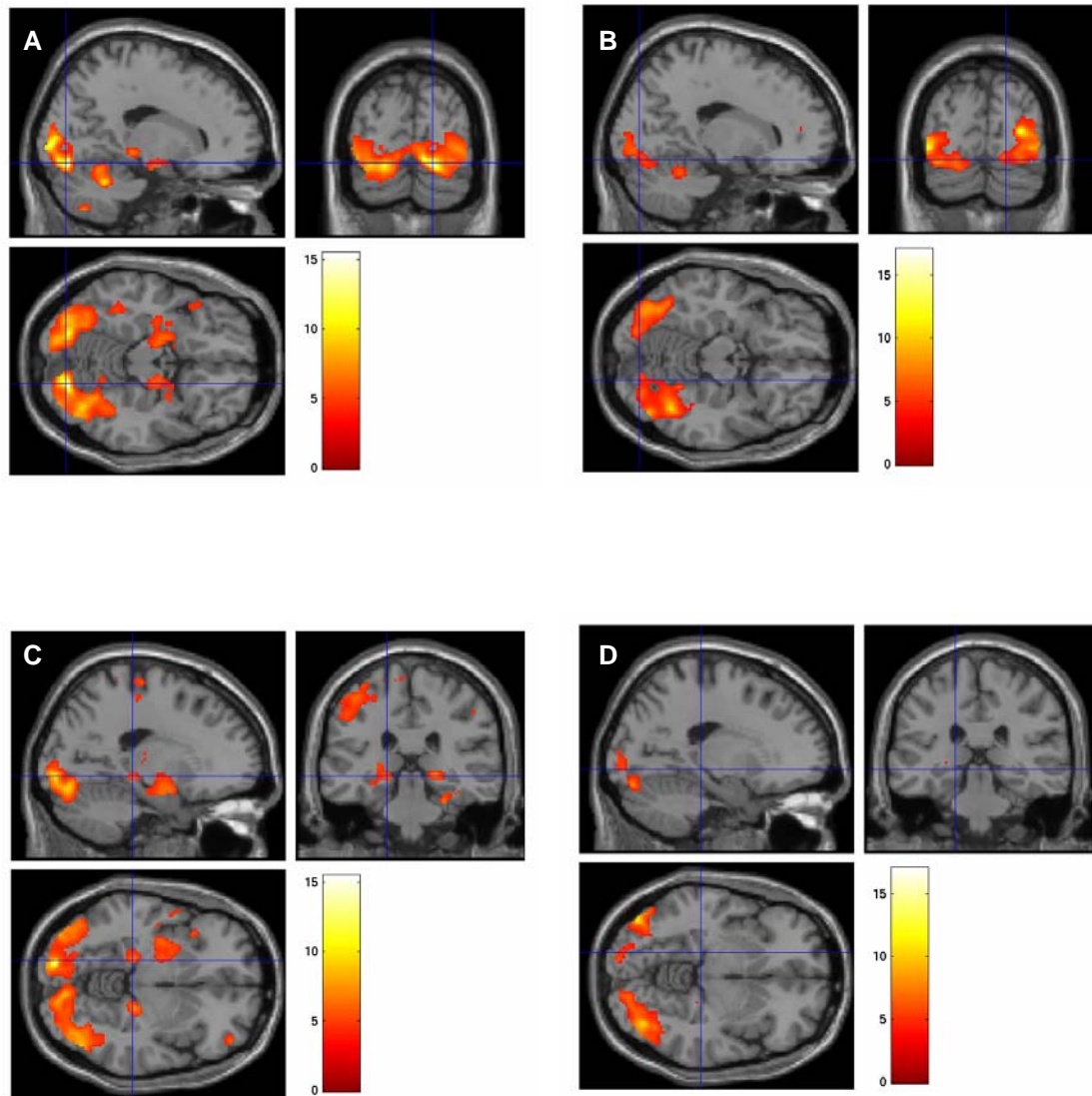


Figure 4.7A - Control fusiform activation in response to fearful body stimuli. B - ASD activity at the same coordinates as A. C – Bilateral hippocampal activation in the control group. D – ASD group map at the same coordinates as C.

4.3.2.3 Isolating emotion (Contrast 3)

Blocks of fearful faces were contrasted with neutral faces to isolate the component of emotion. The control group activated bilateral inferior parietal lobe ($p < 0.001$) and middle frontal lobe ($p < 0.001$ on the right, $p = 0.013$ on the left) in response to emotion. No regions of activation were present in the ASD group. (See table 4.6 and figure 4.8.)

Neither group showed any emotion dependent activation in the body task when analysing only the first run of the task. As outlined above, data from both runs of the task were then combined and analysed. In this analysis, there was a trend in the control group towards significant activation in the superior temporal lobe ($p = 0.081$) and a tendency in the right middle occipital lobe ($p = 0.142$). When a small volume correction was applied to the superior temporal gyrus region, the cluster of activation in the superior temporal lobe was significant ($p = 0.008$). No regions of activity were found in the ASD group. (See table 4.7 and figure 4.9)

When the ASD group was directly contrasted with the control group it was found that when processing emotion from face stimuli the control group had significantly greater activation than the ASD group in the inferior parietal lobe bilaterally ($p = 0.004$ on the right, $p = 0.01$ on the left) and a trend towards greater activation in the left precentral gyrus ($p = 0.072$) (table 4.8 and figure 4.91A). No significant between group differences were apparent when the first run of the body task was analysed. When both runs of the body task were analysed, the control group was found to activate the right supplementary motor area to a greater extent than the ASD group when processing emotion from body stimuli ($p = 0.021$). There was also a trend in the right superior temporal lobe ($p = 0.087$) and a tendency towards a difference in activation in the left superior temporal lobe ($p = 0.163$) (table 4.8 and figure 4.91B).

Contrast 3 - Fear condition vs neutral condition - Faces

Region	Control			x	y	z
	cluster kE	Z score	cluster corrected p			
Left inferior parietal lobe/angular gyrus	366	4.5	<0.001	-38	-66	42
Right inferior parietal lobe	439	4.37	<0.001	46	-52	46
Right middle frontal lobe	739	4.36	<0.001	46	46	4
Left middle frontal lobe	171	4.13	0.013	-42	48	10

Table 4.6 - Within group results for the control group when the fearful face condition is contrasted with the neutral face condition. Only data from the first run of the task analysed. Threshold at 0.001, MNI coordinates displayed. No suprathreshold clusters were found in the ASD group analysis.

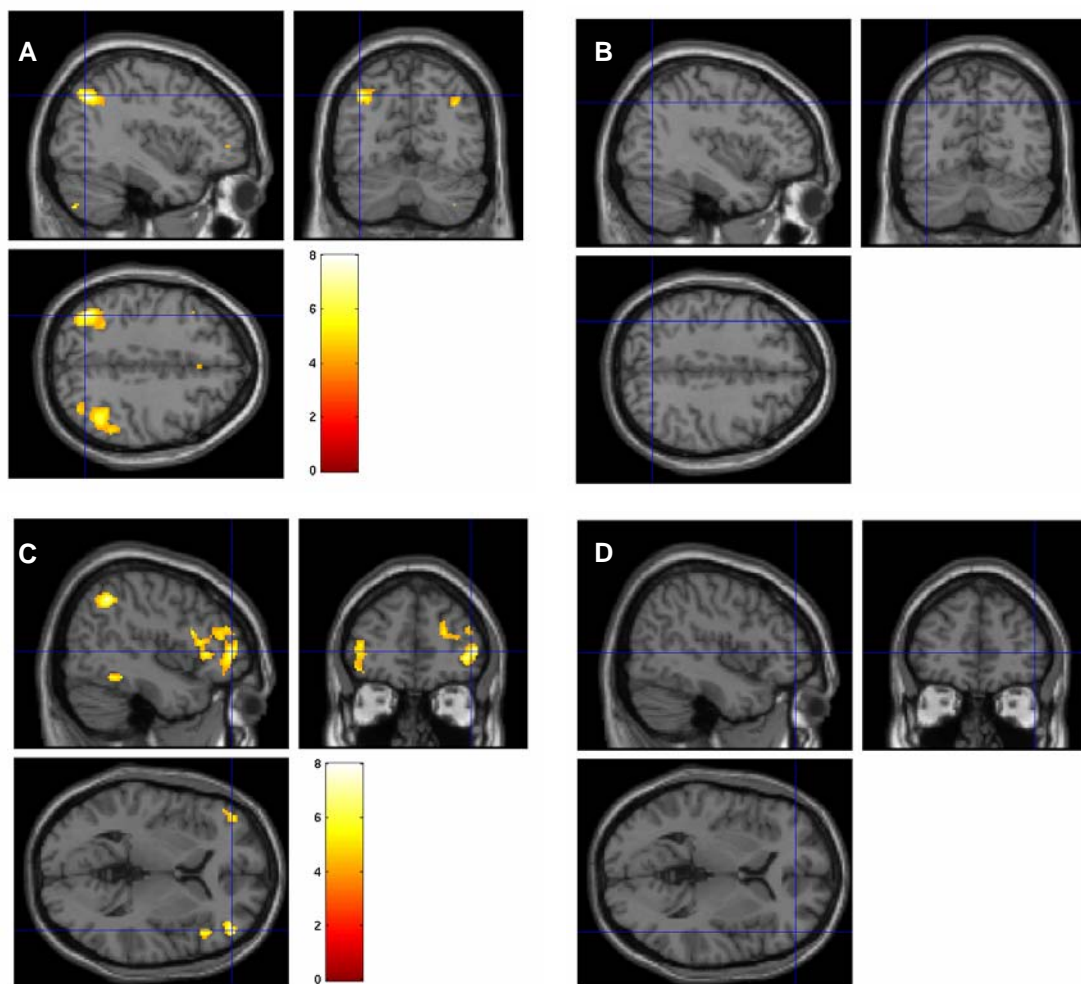


Figure 4.8A - Control group activation in bilateral inferior parietal lobe in response to fearful face stimuli contrasted with neutral faces. B - ASD group map at the same coordinates as A. C – Middle frontal lobe activity in the control group in response to fearful face stimuli contrasted with neutral faces. D – ASD group map at the same coordinates as C. No significant activation in either parietal or frontal lobe was evident in the ASD group, or elsewhere in the brain.

Contrast 3 - Fear condition vs neutral condition - Bodies

Region	Control			X	y	z
	Cluster kE	Z score	cluster corrected p			
Right superior temporal lobe	98	3.81	0.081	48	-18	0
Right middle occipital lobe	82	4.41	0.142	32	-60	38

Table 4.7 - Within group results for the control group when the fearful body condition is contrasted with the neutral body condition. Data from both runs of the task analysed. Threshold at 0.001, MNI coordinates displayed. No suprathreshold clusters were found in the ASD group analysis.

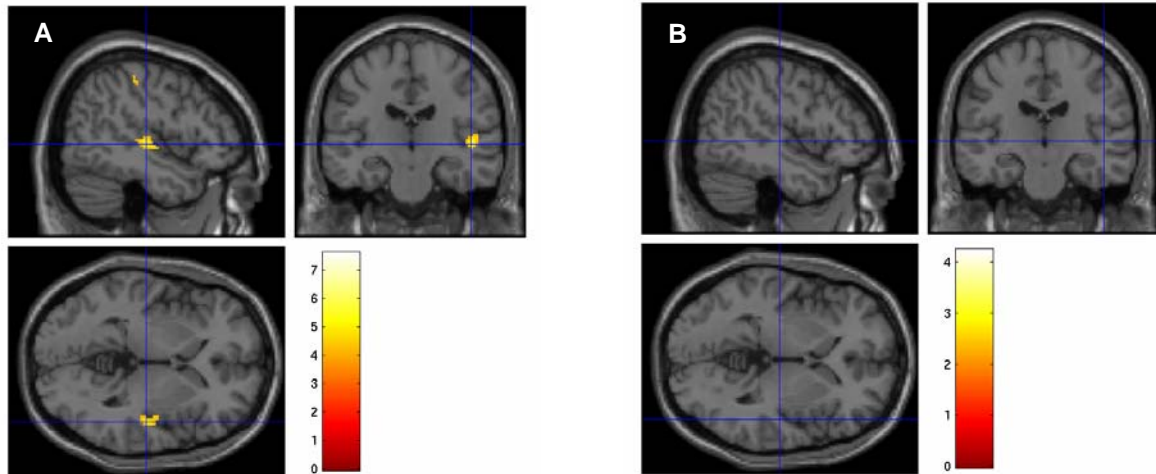


Figure 4.9A - Control group activation in right superior temporal lobe in response to fearful body stimuli contrasted with body stimuli. B - ASD group map at the same coordinates as A. No significant activation was evident in the ASD group anywhere in the brain. Data from both runs of the task analysed.

Contrast 3 - Fear condition vs neutral condition - Control > ASD

Fear Faces vs. Neutral Faces (run 1)						
Region	Cluster kE	Z score	Cluster corrected p	x	y	z
Right inferior parietal lobe	761	3.91	0.004	40	-52	40
Left inferior parietal lobe/angular gyrus	658	3.69	0.01	-38	-60	34
Left precentral gyrus	427	3.93	0.072	-54	2	24

Fear Body vs. Neutral Body (runs 1 and 2)						
Region	Cluster kE	Z score	Cluster corrected p	x	y	z
Right supplementary motor area	513	3.71	0.021	6	-28	66
Right superior temporal lobe	362	3.36	0.087	40	-34	6
Left superior temporal lobe	307	3.96	0.163	-54	-6	2
Left superior temporal lobe	291	3.66	0.191	-60	-40	14

Table 4.8 - Between group results for Control > ASD when the fear face condition is contrasted with the neutral face condition and when the fear body condition is contrasted with the neutral body condition. Threshold at 0.005, MNI coordinates displayed.

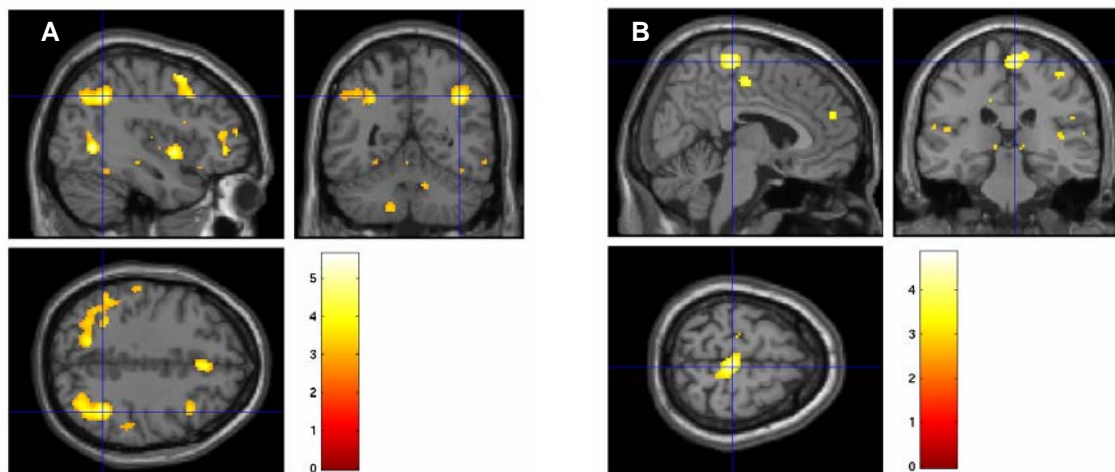


Figure 4.91A – Between group contrast (Control > ASD), fear face condition contrasted with neutral face condition from run1. B - Between group contrast (Control > ASD), fear body condition contrasted with neutral body condition from run1 and run2.

4.3.2.4 Small volume correction analysis

In relation to processing neutral stimuli (both faces and bodies) there were no significant differences in the activation of any of the small volumes specified between the ASD group and the control group.

During processing of fearful faces the ASD group activated significantly less than the control group in the left insula ($p=0.022$) and a tendency towards reduced activation was also found in the right insula ($p=0.176$). There was also a tendency for reduced activation in the ASD group in the left superior temporal lobe ($p=0.146$) and the left amygdala ($p=0.107$). In relation to processing fearful body stimuli, there was a trend in the left superior temporal lobe ($p=0.085$) and the left amygdala ($p=0.054$) for the ASD group to activate this region less than the control group.

When the fear and neutral conditions were contrasted in the faces task, a tendency for reduced activation in the ASD group was found in the right insula ($p=0.11$). In the body task, the component of emotion led to significantly greater activation of bilateral superior temporal lobe in the control group than in the ASD group ($p=0.014$ on the right, $p=0.035$ on the left). A trend for reduced activation in the ASD group relative to the control group was also found in the left insula ($p=0.076$). These findings are summarised in table 4.9.

Small volume correction analysis - Control > ASD

Fear Faces vs. Baseline (run 1)						
Region	Cluster kE	Z score	cluster corrected p	x	y	z
Left insula	208	3.63	0.022	-40	-4	-2
Right insula	59	3.62	0.176	32	-24	12
Left superior temporal lobe	84	3.15	0.146	-40	-6	-8
Left amygdala	8	2.88	0.107	-20	-2	-12
Fear Body vs. Baseline (run 1)						
Region	Cluster kE	Z score	cluster corrected p	x	y	z
Left superior temporal lobe	127	3.33	0.085	-58	-6	-4
Left amygdala	35	3.3	0.054	-20	-6	-14
Fear Faces vs. Neutral Faces (run1)						
Region	Cluster kE	Z score	cluster corrected p	x	y	z
Right insula	93	3.89	0.110	40	2	-4
Fear Body vs. Neutral Body (runs 1 and 2)						
Region	Cluster kE	Z score	cluster corrected p	x	y	z
Left insula	111	3.7	0.076	-42	2	2
Left superior temporal lobe	186	3.66	0.035	-60	-40	14
Right superior temporal lobe	261	3.36	0.014	40	-34	6
Left superior temporal lobe	75	3.96	0.166	-54	-6	2

Table 4.9 – Small volume corrections applied to whole brain analysis of between group differences. Threshold at 0.005, MNI coordinates displayed.

**Summary of group differences
Control > ASD**

		Small volume corrections							
		Fusiform gyrus		Amygdala		Insula		Superior temporal lobe	
		Left	Right	Left	Right	Left	Right	Left	Right
Neutral face vs baseline	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Neutral body vs baseline	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Fear face vs baseline	right lingual gyrus (p=0.163) left insula (p=0.125)	n/s	n/s	p=0.107	n/s	p=0.022	p=0.176	p=0.146	n/s
Fear body vs baseline	right lingual gyrus (p=0.021)	n/s	n/s	p=0.054	n/s	n/s	n/s	p=0.085	n/s
Fear faces vs neutral faces	right parietal lobe (p<0.004) left parietal lobe (p<0.01)	n/s	n/s	n/s	n/s	n/s	p=0.110	n/s	n/s
	left pre central gyrus (p=0.072)								
Fear body vs neutral body	right supplementary motor area (p=0.021)	n/s	n/s	n/s	n/s	p=0.076	n/s	p=0.035	p=0.014
	right superior temporal lobe (p=0.087)								
	left superior temporal lobe (p=0.163)								

Table 4.91 – Summary of between group differences for each contrast in the analysis. In each result presented the control group shows greater activation than the ASD group. ‘n/s’ represents no significant difference between groups. Light blue represents a tendency towards a between group difference $p>0.1$, <0.2 . Blue represents a trend level difference ($p<0.1$). Navy indicates a significant group difference, $p<0.05$.

4.3.2.5 Conjunction analysis

As illustrated in figure 4.92 and 4.93, both the face and body emotion processing tasks resulted in between group differences in similar regions, although these differences do not always meet statistical significance in both tasks. A conjunction analysis was subsequently carried out to explore whether there were regions of significant between group difference that were common to both the face and body task.

When the fear vs baseline contrast was investigated, at a whole brain level there was a tendency for the right lingual gyrus to show aberrant activation in the ASD group in response to emotion in both the face and body task (p corrected = 0.111). A small cluster of non-significant common group difference was also observed in the left amygdala (p corrected = 0.145 when an amygdala small volume correction was applied). These regions of common group difference are illustrated in figure 4.94. No such regions were identified when the more subtle fear vs neutral contrast was investigated.

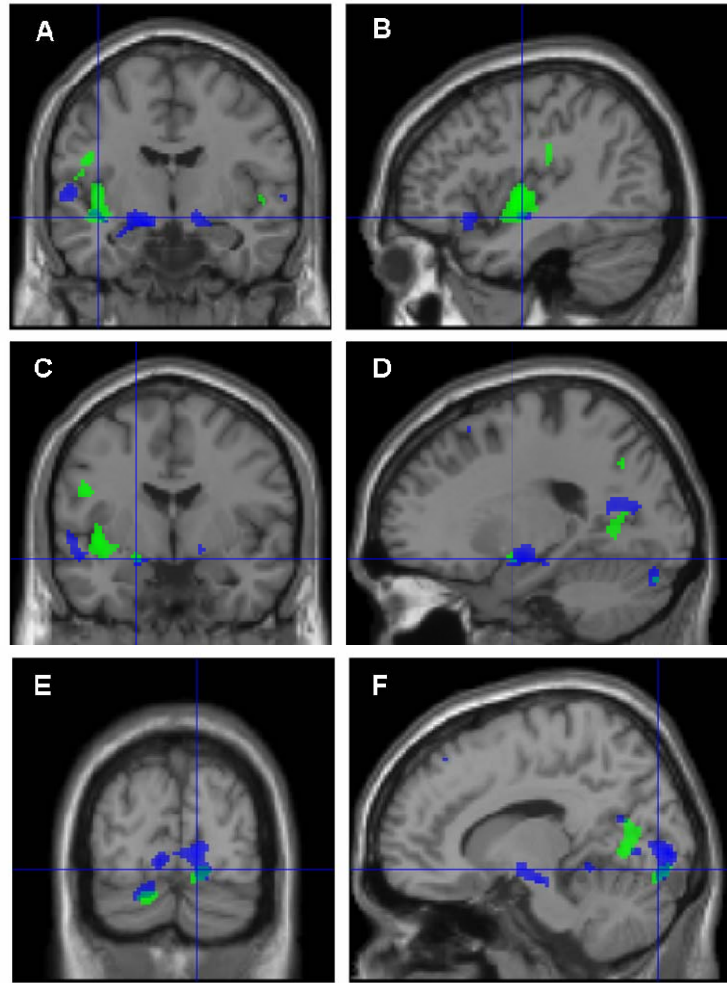


Figure 4.92 – Overlay of between group differences when fear face processing is contrasted with fixation baseline (green) and fear body processing is contrasted with fixation baseline (blue). Panels A and B illustrate the coronal and sagittal view of the left superior temporal lobe. Panels C and D illustrate the coronal and sagittal view of the left amygdala. Panels E and F illustrated the coronal and sagittal view of the right lingual gyrus.

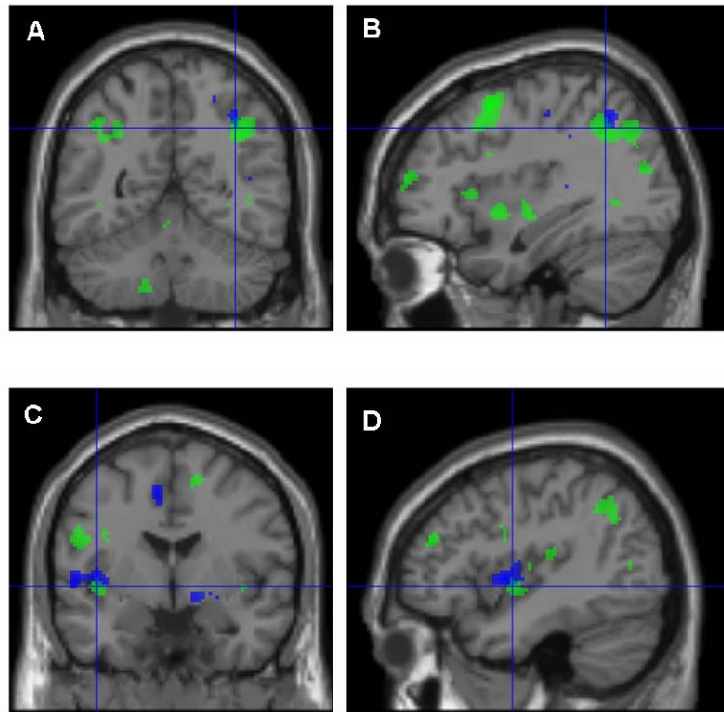


Figure 4.93 – Overlay of between group differences when fear face processing is contrasted with neutral face processing (green) and fear body processing is contrasted with neutral body processing (blue). Panels A and B illustrate the coronal and sagittal view of the right inferior parietal lobe at 36, -54, 40. Panels C and D illustrate the coronal and sagittal view of the left superior temporal lobe at -41, -3, -2.

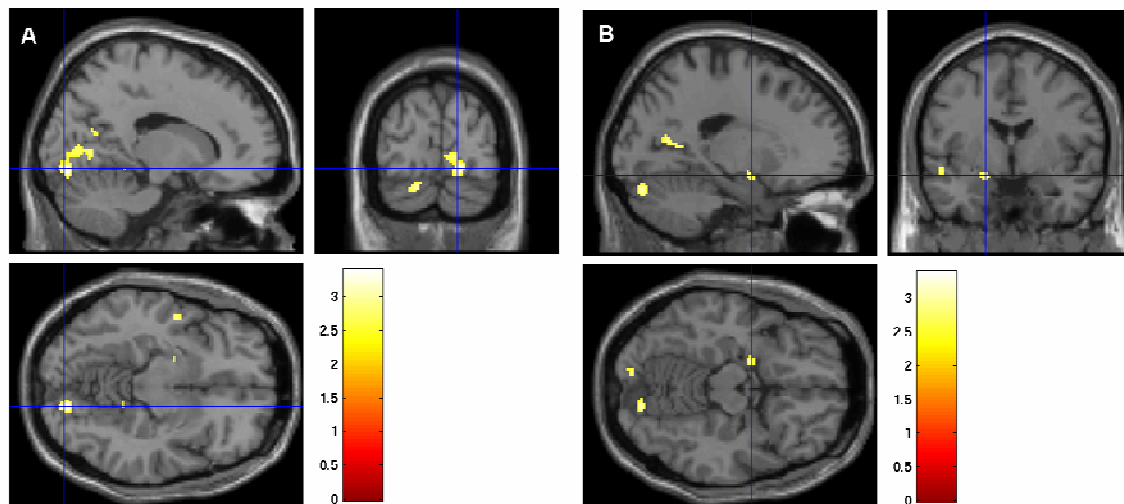


Figure 4.94 – Results of the conjunction analysis. A) The region of right lingual gyrus (MNI coordinates 16 -86 -10) which activated differently in the ASD group compared to controls when processing both fearful faces and bodies contrasted with fixation baseline. B) The region of left amygdala (MNI coordinates -18 -2 -14) which activated differently in the ASD group compared to controls when processing both fearful faces and bodies contrasted with fixation baseline.

Threshold set at 0.005.

4.3.2.6 Effect of ADOS score

Values were extracted from clusters of significant between group difference as carried out in the primary analysis. These were the right and left inferior parietal lobe in the fearful faces vs neutral faces contrast and supplementary motor area in the fearful body vs neutral body contrast. Results of the ANOVA revealed a significant effect of group ($p=0.001$ for the right inferior parietal lobe and supplementary motor area and $p<0.001$ for the left inferior parietal lobe). Applying t-tests to explore the effect of group demonstrated that in each region, the control group had significantly higher activation than both the ADOS positive group and the ADOS negative group. Furthermore, there were no significant group differences between the values extracted for the ADOS positive or ADOS negative groups as illustrated in figure 4.95.

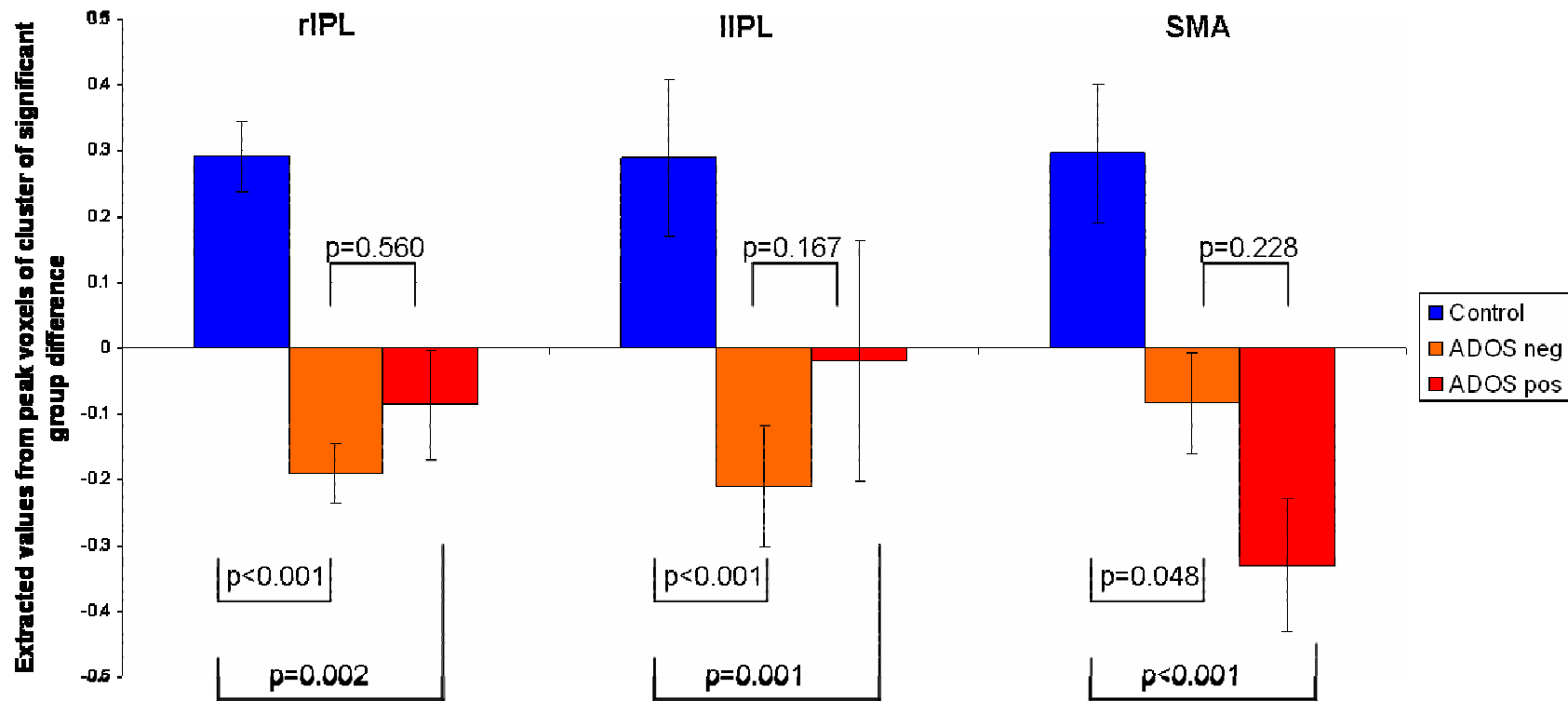


Figure 4.95 – Results of independent t-test of extracted values from peak voxels of between group difference. rIPL – right inferior parietal lobe, lIPL – left inferior parietal lobe, SMA – supplementary motor area. Standard error bars are displayed.

4.4 Discussion

It was hypothesised that there would be differences between groups in the neural response to neutral face and body stimuli. Whilst there were qualitative differences in the within group activation maps in response to neutral stimuli, no significant group differences were found to support this hypothesis. It was also hypothesised that deficits in relation to the processing of emotional content in both stimulus types would be found in the ASD group and that these would lie in regions of the social brain. Indeed the fear vs baseline and the fear vs neutral contrast resulted in significant between group differences in both tasks in the predicted neural network. Finally, in support of a common neural substrate underlying a global emotion processing deficit in ASD it was predicted that regions of group difference found in each task would overlap. Qualitative inspection of between group maps and the conjunction analysis provide some support for this final hypothesis.

It is also of note that all group differences were found in the same direction; the control group activation was always greater than that of the ASD group. Both groups performed the task successfully and there were no behavioural performance differences. Finally, in both the control and ASD group the tasks resulted in activation in sensible regions in line with previous studies using similar paradigms.

4.4.1 Summary of findings

When processing neutral stimuli, presented as face or whole body images, both the control and ASD group recruited similar networks of brain activation, i.e. there were no significant differences in the between group analysis or subsequent analyses where small volume corrections were applied.

In relation to the emotional stimuli the control group activated the amygdala/hippocampal complex in response to fear presented in faces and bodies. This effect was not observed in the ASD group. When the groups were directly contrasted in a whole brain analysis a region of the right lingual gyrus activated significantly differently in response to fearful body stimuli and a trend for this same region to activate differently was also seen in response to fearful faces. When small volume corrections were applied to the whole

brain analysis, there was a trend in the left superior temporal lobe and the left amygdala for the ASD group to activate less than the control group in response to both fearful face and body stimuli. These similar regions of between group difference when processing fear from both faces and whole body images were explored further in the conjunction analysis and are illustrated in figure 4.92 and 4.94.

In response to the isolated component of emotion (fearful stimuli contrasted with neutral stimuli), regions of brain activity were modulated by emotion in the control group but this was not seen in the ASD group. This was evident in the between group contrast; bilateral inferior parietal lobe activated significantly differently between groups in response to facial emotion; right supplementary motor area activated significantly differently between groups in response to emotion portrayed in whole body images and the application of small volume corrections revealed further differences in bilateral superior temporal lobe. Again, when the between group maps from both the face and body tasks are overlaid, there is overlap in clusters of group difference (figure 4.93).

4.4.2 Interpretation of findings

4.4.2.1 Basic processing of neutral social stimuli

The control group demonstrated a predictable pattern of bilateral fusiform gyrus activation in response to neutral face stimuli. Qualitatively, the ASD group showed a more disorganised pattern of activation and the peak activity is more inferior to that seen in the control group, located in the cerebellum. This may be representative of a less well defined fusiform face area, so whilst the fusiform does respond to face stimuli in ASD, the specialisation of this region has not developed. This is supported by the behavioural data presented in chapter 3 in which the significantly poorer performance in the ASD group of judging identity, emotion and other social features from faces is indicative of these individuals not having developed expertise in face processing. Previous studies have also reported less focal fusiform gyrus activation during face processing in ASD; Pierce et al (2001) reported that ASD participants displayed peak activations in a range of brain regions including areas of frontal lobe and cerebellum in contrast to control participants in which peak activity was always within the fusiform gyrus.

The control group have a region of peak activation in right lingual/fusiform gyrus which occurs in response to both neutral face and body stimuli suggesting that the recognition of various social cues is mediated by a very similar neural substrate across modalities as suggested by previous literature (Hadjikhani and de Gelder, 2003, van de Riet *et al.*, 2009). When processing body stimuli however, the control group activated additional regions that were not seen during face processing. This included the bilateral hippocampus and regions previously reported to activate in response to biological motion; the supplementary motor area and the precentral gyrus. In the previous studies which investigated processing of static neutral body images as looked at here, a contrast in which neutral body stimuli were compared with a baseline condition was not reported (Hadjikhani and de Gelder, 2003, van de Riet *et al.*, 2009).

The ASD group activated less extensively than the control group when processing neutral body stimuli; significant activation was limited to the occipital cortex. Areas of activation apparent in the control group in regions associated with mirror neuron activity (supplementary motor area and the precentral gyrus) showed no significant activity in the ASD group. Also, as seen in the analysis of neutral face processing, the peak activation in the ASD group is displaced compared to the control group. As in the case of face processing, this may reflect a failure to develop a focal region of neuronal activity in line with behavioural expertise in processing that specific class of stimuli. However direct comparison of the ASD and control group, even using small volume corrections, failed to reveal any significant differences in brain activation in response to neutral stimuli.

4.4.2.2 Processing emotional face stimuli

Both the control group and the ASD group activated face processing regions in response to fearful face stimuli; right fusiform gyrus and left lingual gyrus. Both groups also activated the right inferior frontal gyrus, part of the extended network involved in emotion processing (Brothers, 1996).

The control group significantly activated left insula and amygdala in response to fearful faces which is consistent with previous reports of amygdala response to fearful stimuli in the left hemisphere and the role of the insula in emotion processing. This was not seen in the ASD group. The ASD group however, activate right middle occipital cortex and the left precentral gyrus. This suggests less emotion specific activation in the ASD group; even though the ASD group respond more strongly in visual processing regions (more activity in occipital cortex), regions associated with emotion processing (amygdala) are not recruited. This is consistent with previous reports of relative hypoactivation of the amygdala in response to facial emotion in ASD (Ashwin *et al.*, 2007a, Baron-Cohen *et al.*, 1999, Critchley *et al.*, 2000, Dalton *et al.*, 2005, Wang *et al.*, 2004).

However Dalton et al (2005) also reported eye tracking data which demonstrated that the ASD group spent less time fixating on the eye region of face stimuli. He proposed that the amygdala hypoactivation in the ASD group was a result of the ASD participants not scanning the faces in the same manner and attending to the same features as the control group and therefore not processing the signals which communicate emotion. Without eye tracking data in this study it is impossible to distinguish whether differences in scan path could account for the failure of the amygdala to activate, or rather that the amygdala in these participants is unresponsive to emotional cues. Whilst initially findings from Dalton et al (2005) seem persuasive they cannot account for the amygdala hypoactivation reported by Baron-Cohen et al (1999) during a social cognition task in which the only visual stimuli presented was the eye region of faces.

4.4.2.3 Processing emotional body stimuli

In the body task, the control group again activate the fusiform, as well as the pre- and post central gyrus, left superior temporal lobe and bilateral hippocampus as seen during neutral body processing. Again, activity in the ASD group was limited to bilateral occipital lobe. Due to the nature of the stimuli used in this task, in which faces and eyes were not visible within the whole body image, even without eye tracking data, it can be assumed that the different neural response in the two groups cannot be attributed to the failure of the ASD group to scan and process eyes.

Of note is also the similar pattern of between group differences seen in response to emotional faces and bodies. During both tasks, between group differences were observed in the right lingual gyrus, left amygdala and left superior temporal lobe (figure 4.91). Although non-significant, the conjunction analysis suggested that there are regions of difference common to both tasks: the right lingual gyrus and left amygdala. The convergence of results from both tasks supports the idea that the deficits in emotion processing seen in ASD are mediated by a difference in neuronal activation that is specific to emotion, and not the type of social stimuli presented.

4.4.2.4 Isolating emotion

The control group activated bilateral inferior parietal lobe and middle frontal lobe in response to facial emotion; both regions associated with the social brain network (Brothers, 1996). No regions were differentially activated by emotion in the ASD group.

When the ASD group was directly contrasted with the control group it was found that when processing emotion from face stimuli the control group had significantly greater activation than the ASD group in the inferior parietal lobe bilaterally. As mentioned above, it has been reported that within the inferior parietal lobe there are a population of mirror neurons which are thought to mediate self- other- mapping. More specifically, activation of bilateral parietal lobe has been reported during the processing of emotional faces when control participants were asked to focus on their own emotional response relative to the perceived face (Schulte-Rüther et al., 2007). The results in the current study indicate that even during passive viewing, facial emotion induces brain activity related to empathy in the control group, and that this activation was not seen in the ASD group.

Neither group showed any emotion dependent activation in the body task when analysing only the first run of the task. As outlined in the methods section (4.2.3.3), data from both runs of the task were then combined and analysed. In this analysis, there was a trend in the control group towards significant activation in the right middle occipital and superior

temporal lobe – a region reported to be involved in movement perception. In contrast to previous work (Hadjikhani and de Gelder, 2003, van de Riet *et al.*, 2009) increased fusiform and amygdala activity was not seen. Differences in study design may account for this; in the current study stimuli were presented for a shorter duration and a block design was implemented rather than interspersing the emotion type presented. Finally, participants passively viewed the stimuli indicating only the appearance of the next image rather than making explicit judgements on the emotional content of images. Again, as in the face processing task no significant activation was observed in the ASD group in response to emotion.

In a between group analysis, when both runs of the body task were analysed, the control group was found to activate the right supplementary motor area to a greater extent than the ASD group when processing emotion from body stimuli.

Whilst contrasting fear and neutral stimuli in each task revealed between group differences in different anatomical regions there is convergence in the function of the inferior parietal lobe and superior temporal sulcus region as both are considered components of the Social Brain. Further to this, when the between group maps are overlaid (figure 4.94) a cluster of between group difference can be seen in the inferior parietal lobe in the body task and in the superior temporal lobe in the faces task. Whilst these clusters fail to reach statistical thresholds, they support the idea that similar neural substrates are involved in ASD in relation to deficits in emotion processing which supercede basic differences in processing style or stimulus type.

4.5 Conclusion

In support of the first hypothesis, the patterns of activation induced by neutral social stimuli differed qualitatively between the control and ASD group. The fusiform activation in the ASD group appeared less focussed during face processing, and the neural response to body stimuli was atypical also. This lends support to the idea that the individuals with ASD have a widespread deficit in the processing of social cues, not isolated to a face processing dysfunction.

Differences between groups which reached statistical significance were apparent when analysing the neural response to emotional stimuli. This was found in relation to both face and body stimuli and in similar neuroanatomy. Therefore the aberrant response to emotional stimuli seen in the ASD group cannot be accounted for by individuals with ASD failing to process eyes.

Brain regions which activated significantly differently between the ASD and control group during emotion processing were found in areas regarded to be within 'the social brain'. Furthermore, qualitative comparison of the between group maps from the face and body tasks suggested that there are regions which activate differently in response to emotion in the ASD group regardless of the stimulus type presented.

Chapter 5 - General Discussion

5.1 Introduction

Within this thesis, a thorough review of relevant literature and the acquisition of both behavioural and neuroimaging data has been carried out in order to investigate emotion processing in ASD. In this chapter an overview of the study is provided and the results from each chapter will be summarised and integrated. Methodological strengths and limitations will be discussed and suggestions for further work outlined.

5.2 Study overview

Whilst evidence exists to suggest that autism is not a modern day phenomenon, it is relatively recently that Autism Spectrum Disorders have been recognised as a neurodevelopmental condition and investigated accordingly. A core diagnostic feature of ASD is the presence of deficits within social communication and understanding and as such investigating emotion processing in individuals with ASD is of paramount importance.

Systematically reviewing previous fMRI studies of ASD identified that in relation to the investigation of emotion there has been a bias towards using face stimuli. The literature not only demonstrates a neglect of the study of other emotional cues but also identifies a number of confounds involved in studying faces (scan path, task demands) that are yet to be reconciled. Furthermore, few studies have been designed and analysed in such a way that emotion processing can be investigated without basic face processing deficits confounding findings.

The bias towards studying faces at the expense of the investigation of additional emotional cues influenced the design of the behavioural study carried out here. Emotion processing was investigated from diverse social cues; stimuli were presented in both the visual and auditory sensory domain, both static and dynamic stimuli were investigated and a range of basic emotions were included. The results indicated a global emotion processing deficit with the ASD group performing significantly worse than the control group at recognising a range of basic emotions from each stimulus type.

The broad ranging deficits observed in the ASD group when processing emotions from all stimulus types influenced the design of the functional imaging component of the project. The neural response to both neutral and emotional stimuli was of interest, but importantly this was not just investigated using face stimuli but also emotion represented in whole body gestures.

When processing neutral stimuli both groups broadly recruited the expected network of brain regions. When qualitatively comparing the within group maps in response to neutral face stimuli, the ASD group activation appeared less focussed within the fusiform gyrus. The within group activation maps produced in response to neutral whole body stimuli demonstrated a lack of activation in the ASD group of the extended network seen in the control group. However, there were no significant between group differences to either neutral faces or whole body stances when the groups were directly compared, even when small volume corrections were applied. In response to emotional faces and whole body stances, the control group activated regions involved in emotion processing including the amygdalohippocampal complex, an effect not present within the ASD group activation map. Again, the direct comparison of the groups in response to emotional faces or whole body gestures revealed no significant differences. Application of a small volume correction to the amygdala did however reveal trend level differences between the groups; the ASD group activated the left amygdala to a lesser extent than the control group in response to both fearful face and body stimuli.

As the task was designed in such a way that the neutral and emotional stimuli were presented as separate conditions, the isolation of the component of emotion within the analysis was possible. When the emotional condition was contrasted with the neutral condition for both stimulus types, the control group was seen to differentially activate social brain regions in response to the emotional content. This effect is not seen in the ASD group and indeed the value of this design becomes apparent when direct group comparisons were carried out on these contrasts. In response to facial emotion, activation in the bilateral inferior parietal lobe differs significantly between groups at a whole brain level. When emotion portrayed in whole body gestures is isolated and compared between

groups, activity in the supplementary motor area and superior temporal sulcus region differs significantly. Notably, the inferior parietal lobe and the superior temporal sulcus region are components of the social brain network and the inferior parietal lobe is thought to contain mirror neurons and mediate self-other perception.

In summary, this study has demonstrated both behavioural and neurophysiological deficits in processing emotion across stimulus modalities, suggestive of a global deficit in emotion processing in ASD mediated by aberrant activity in social brain regions, potentially resultant from mirror neuron dysfunction. The broad ranging behavioural deficits and neuronal dysfunction seen in this study during relatively simple tasks in a cohort of about average IQ, illustrates the depth and magnitude of the social processing deficits in ASD.

5.3 Strengths and limitations

5.3.1 Overcoming recruitment difficulties inherent to ASD

Investigating individuals with ASD presents some inherent difficulties. As a lifelong condition with no current treatment, many adults with ASD will have no reason to be in contact with medical professionals in contrast to other clinical populations such as those with schizophrenia. Therefore unlike previous studies within the Division of Psychiatry where most study participants can be recruited via clinicians involved in the study, in this instance we formed links with a voluntary sector service; Number 6. This provided us with access to a large sample with which to recruit from and also meant that we could meet with and complete the behavioural study protocol with participants in an environment where they already felt comfortable, reducing the stress and anxiety associated with meeting new people in a new environment which many people with ASD feel. This successful way of recruiting and testing participants is reflected by the 100% attendance rate for appointments and 0% drop out rate from the study. The successful recruitment strategy is also reflected by the sample size of the study. Twenty three ASD participants took part in the behavioural study and 13 in the imaging study. These represent reasonably large study samples in comparison to previous behavioural and imaging studies of ASD.

As described above, the ASD study participants were recruited via Number6 - a drop in centre which provides a range of services to adults with 'high functioning autism and Asperger Syndrome' but primarily facilitates social groups and activities. As such, the cohort recruited represent a subset of individuals with ASD that are actively seeking support and social contact which may not be representative of the ASD population more generally. Future studies will also recruit from the clinical diagnostic regional ASD service, providing a broader sample of individuals with ASD. Also, to increase how representative the sample is, ideally the study would have included individuals with ASD and intellectual impairment – however this would have required the re-design and/or exclusion of some of the protocol due to the level of demands required. Within the behavioural study both male and female participants were included but only male participants have been included in the imaging study.

5.3.2 Successful completion of the scan procedure

As previously outlined, participating in an hour long experimental protocol in an MR scanner may be particularly challenging for an individual affected by ASD. The additional preparation outlined in the methods of chapter 4 appeared to be successful as all participants invited for a MRI scan successfully completed the procedure. Additionally, no within scanner behavioural performance differences between groups that could account for the imaging findings were apparent.

5.3.3 Strengths and limitations of experimental design

There have been studies of emotion processing in ASD which have used stimuli other than faces, yet there appears to be no study which has investigated more than one stimulus modality within the same ASD sample. The only studies which have included more than one stimulus modality within their experiment have combined these within the one experimental condition e.g. when Wang et al (2006) investigated irony perception. This is true both of the behavioural and imaging literature. In this study, within the same sample of individuals with ASD, we collected behavioural data assessing participants' ability to process emotions from face, gesture and vocal stimuli. Similarly, we are the

first group to our knowledge to carry out an fMRI investigation of emotion processing of two stimulus types in the same sample of individuals with ASD. Furthermore, the design of the imaging tasks applied in this study allowed us to distinguish between basic processing of neutral social stimuli and the effect of emotional content.

This study was the first fMRI investigation of an ASD cohort to be carried out in the Division of Psychiatry. Consequently a paradigm was selected that was not only relevant to the clinical group, but had also already been shown to be a task that provided robust activation of the neural circuitry of interest. In addition, the task selected had been completed by another clinical group (patients with schizophrenia) suggesting that it was a paradigm that an ASD group would also be able to carry out. The task requirements were simple (button press in response to appearance of a new stimulus) and indeed all ASD participants successfully completed the paradigm. In future studies however, it may be preferable to use a more challenging task e.g. asking participants to make a decision on the stimuli or perform a working memory task. This would ensure participants engage more with the stimuli and more tightly constrains the possible cognitive processes taking place. As it has been previously suggested that differences in scan path in ASD participants may account for differences in their neural response to faces, using shorter stimulus durations could reduce the likelihood that this variable may be influencing the imaging findings. Using shorter stimulus durations could also reduce the level of neuronal habituation to emotional stimuli that has been seen previously and may be relevant to this data. Indeed an event related design would further reduce issues of neuronal habituation.

5.3.4 Cross modal basic processing tasks

The use of various stimulus domains was included in the behavioural protocol to establish whether the emotion processing deficits reported in the literature were specific to face stimuli and resultant of a specific face processing deficit. Whilst the cross modal emotion processing deficits reported support a global emotion recognition dysfunction in ASD, it is of note that more basic deficits in face processing were also apparent. Whilst a basic face processing deficit cannot alone account for the broad range of cross modal

difficulties, problems with basic processing cannot be discounted. It may be that basic processing deficits of social stimuli exist regardless of emotion, across modalities. To address this, further tasks would be required for example an auditory equivalent to the Benton Task of Facial Recognition.

5.3.5 Assumptions about ‘emotion’ and ‘neutral’

Emotion is not binary and whilst for the purposes of experimental design conceptually the fear condition is regarded as ‘1’ and the neutral condition as ‘0’, in reality these conditions really represent end points of a scale of emotionality. Many social stimuli convey a level of emotion, and even low level or ‘neutral’ emotion is informative when it comes to interpreting and interacting in a social situation. It is also important to consider in regard to this the environmental validity of using such extreme examples of emotion. Especially when investigating a population known to have difficulties in processing emotional stimuli, potentially as a result of experiential factors, using stimuli in which faces and bodies express prototypical levels of emotion rarely expressed in the natural environment may further exacerbate these difficulties.

Also, the neural response to increasing levels of emotion will likely not be a simple one. So it may not be reasonable to conclude that just because deficits in ‘neutral’ processing don’t fully account for deficits in ‘emotion’ processing that there is a specific emotion processing deficit. When taking into account that the ‘emotion’ and ‘neutral’ conditions represent points on a scale of emotionality, is the contrast of ‘fear’ vs ‘neutral’ actually allowing us to isolate emotion processing? Rather than interpreting these results as the ASD group failing to respond to emotion, it would seem more appropriate to conclude that the ASD group fail to modulate brain activity in response to emotion to the same extent as the control group.

5.4 Further planned analysis

The imaging data already collected will also undergo structural analysis. The structural T1 image will be analysed using Voxel Based Morphometry (VBM) to assess grey matter density in the ASD sample compared with controls. In addition, other automated

structural measures developed within the Division of Psychiatry will be applied to the sample; cortical folding will be measured using the Gyrification Index (Bonnici *et al.*, 2007), and automated parcellation of temporal lobe structures will allow for the volume of anatomical regions to be compared.

Functional connectivity analysis is also planned to investigate how activity within the social brain network is modulated in this ASD sample. There is an increasing number of reports of reduced functional connectivity in ASD (Bird *et al.*, 2006, Castelli *et al.*, 2002, Cherkassky *et al.*, 2006, Just *et al.*, 2006, Just *et al.*, 2004, Kana *et al.*, 2006, Kana *et al.*, 2007, Kleinhans *et al.*, 2008, Koshino *et al.*, 2005, Villalobos *et al.*, 2005, Welchew *et al.*, 2005).

5.5 How these findings fit with theories of ASD

5.5.1 Evidence for a global emotion deficit in ASD

This study provides behavioural and imaging evidence to support a global emotion processing deficit in ASD. Firstly, the ASD group demonstrated deficits in processing a range of basic emotions from a variety of stimulus types in both the visual and auditory sensory domain. This does not exclude the possibility that there are basic level deficits in relation to specific stimulus types and in fact the behavioural data presented here supports a basic face processing dysfunction in ASD. The cross modal emotion deficits suggest however that there is a deficit in processing emotion in ASD, over and above the differences which may exist within particular categories of stimuli.

Secondly, the imaging data presented supports an emotion processing deficit in ASD which is again greater than any stimulus specific dysfunction. Whilst qualitative differences were observed when the within group maps of activation to neutral stimuli were compared, no significant differences in brain activation were observed when the ASD group was directly contrasted with the control group. However group differences were apparent when the neural response to fearful stimuli was investigated. Furthermore, a similar network of regions was found to activate to a lesser extent in the ASD group in

response to fear regardless of the stimulus type presented, suggesting that a common neural substrate mediates the emotion processing deficits seen in ASD.

Finally, contrasting fearful faces with neutral faces and fearful bodies with neutral bodies allowed the component of emotion to be isolated and the effect of the stimulus type to be subtracted. In both these contrasts the ASD group failed to modulate social brain regions as seen in the control group. Significant between group differences were apparent and whilst the anatomical loci of these differences were different between stimulus types, between group differences lay in regions of the social brain. The qualitative comparison of the between group maps revealed that clusters of between group difference were shared between tasks but were below threshold. This may be due to insufficient power relating to sample size, the relative salience of the stimuli used or due to the conservative nature of the conjunction analysis employed. Prototypical expressions of fear were used in both the face and body task however no behavioural data was collected to investigate whether both stimulus sets were perceived as equally fearful. Future cross modal emotion studies would need to ensure that stimulus sets were matched for emotional salience.

5.52 Mirror neurons as the neural substrate of impairments in ASD

The most consistently reported region of aberrant activity in fMRI studies of ASD has been the inferior frontal gyrus; a region thought to contain mirror neurons. Whilst the inferior frontal gyrus was not a task activated region in the imaging study reported here, the region of significant between group difference when emotion was isolated face stimuli was a region thought to contain mirror neurons.

Mirror neurons are populations of neurons found throughout the brain which make up the Mirror Neuron System (MNS). Originally discovered in the macaque monkey, single cell recordings revealed that a mirror neuron would fire in response to both the execution *and* the observation of specific goal directed actions. Single cell recording studies in monkeys and fMRI studies in humans exist to support the idea that populations of neurons with this property are found in a range of anatomical regions making up the MNS

(Gallese *et al.*, 1996, Iacoboni *et al.*, 2005). These regions include the inferior frontal gyrus and inferior parietal lobe. Of interest is that within studies in monkeys, mirror neurons were only found to respond to goal directed actions, suggesting that a key element in mirror neuron function relates to the intention of an action and not simply the visual experience. Indeed when considering how infrequently we observe ourselves mirror neurons cannot simply be firing in response to the matching of visual stimuli. The idea of mirror neurons mediating ‘intention matching’ rather than ‘action matching’ is further supported by recent evidence which suggests that mirror neurons may be involved with the matching of emotional experience, thus mediating empathy (Carr *et al.*, 2003, Gallese, 2003). Indeed activation of the inferior frontal gyrus has been shown to correlate with participants empathy scores (Kaplan and Iacoboni, 2006). There is also evidence to indicate that mirror neurons act across sensory domains; audiovisual mirror neurons have been identified in macaque monkeys which fire when the monkey carries out a specific goal directed action, when they observe another carrying out that same action and even when the visual stimulus is blocked but auditory cues are present providing evidence that the action is being carried out (Kohler *et al.*, 2002).

Both fMRI and EEG evidence has been published supporting aberrant activity of regions known to contain neurons with mirroring properties in samples of individuals with ASD (Dapretto *et al.*, 2006, Oberman *et al.*, 2005, Williams *et al.*, 2006). Furthermore, the behavioural evidence for a cross modal emotion processing deficit presented here is consistent with mirror neuron dysfunction in ASD. Not only is there evidence to support the role of MNS in understanding emotions, but mirror neurons have been identified which respond to intentions across sensory modalities (Kohler *et al.*, 2002).

There are also further theoretical arguments which support a MNS dysfunction in ASD. Firstly, mirror neurons respond in a manner that is ‘implicit, unconscious and automatic’ (Gallese, 2003). Therefore dysfunction of such a system could account for discrepancy found in many people with ASD who can consciously and cognitively infer the thoughts and feelings of others but fail to do so automatically. Secondly, there is robust evidence that imitation skills are impaired in children with autism (Williams *et al.*, 2004).

Whilst so far MNS dysfunction has been considered with regard to the social impairments seen in ASD there is a theoretical link between mirror neuron function and language development. Imitation skills are imperative to successful language acquisition, thus it is clear how impairments in imitation could lead to difficulties in language seen in many children with autism. However many individuals with High Function Autism/Asperger Syndrome have much more subtle language impairments. These generally manifest as idiosyncratic choices of vocabulary, unusual tone or volume of speech and an overall unusual feel to their communication style. Yet to be investigated, it may be that the difficulty in defining oddness of language in those with High Function Autism/Asperger Syndrome is attributable to subtle deficits in mirroring. In normal conversation, speakers unconsciously mirror each others' speech on a number of levels; they make the same vocabulary choices, speak at similar rates and even use matching syntax structure. This is thought to help lead to common understanding and therefore effective communication (Branigan *et al.*, 2000, Pickering and Branigan, 1999). One can hypothesise how mirror neurons may mediate such a process and therefore how mirror neuron dysfunction in ASD could account not only for deficits in social understanding, but also the impairments seen in language.

It is less obvious how MNS dysfunction could account for the unusual and restricted interests seen in individuals with ASD. However, if one assumes that mirror neurons are dysfunctional rather than absent it may be that rather than acting to mediate understanding between an individual and other people, in ASD mirror neurons may lead to inappropriate empathising with objects leading to unusual, obsessive and consuming interests.

It is also of note that in addition to the studies referred to above supporting MNS dysfunction in ASD, there is also evidence that the ability to understand and imitate goal directed hand movements is intact in children with ASD. Hamilton et al (2007) failed to find deficits in a group of children with ASD when carrying out imitation and gesture recognition tasks, yet these individuals were impaired in Theory of Mind tasks. The Mirror Neuron System has been proposed to mediate many functions, and this evidence

suggests that perhaps not all Mirror System mediated processes are impaired in ASD and further work is required to better define which aspects of self- other-mapping are disrupted in autism.

There are indeed further limitations to the MNS dysfunction theory of ASD. Firstly, at present, the theory is novel and largely untested in humans. It is also a substantial methodological leap from cellular recordings in monkeys to macroscopic fMRI studies in humans and these imaging studies are still relatively few in number. Further to this, ASD is a developmental disorder and at present nothing is known in regard to the typical development of the MNS. The theory does however have potential in that it appears to be the first theory with a neuronal basis and the possibility to account for the profile of impairments characteristic of ASD.

5.6 Conclusion

A core feature of ASD relates to the processing and interpretation of social signals. This study suggests these deficits are broad and have a neuronal basis. Whilst deficits have been identified at both basic and more demanding levels of social processing, it is clear that the ASD population studied have deficits that are wide ranging and not isolated to a specific emotion or stimulus type. This and several other imaging findings suggest that regions of the social brain respond to emotional and social cues differently in ASD. Moreover, this is in keeping with studies in which elements of the mirror neuron system have been shown to function atypically in ASD.

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Appendix 1 - Guidelines for Research at Number 6

Guidelines for Research at Number 6

A model of good practice

Guidelines on conducting research alongside Number 6

Introduction

It is fundamental to the success of Number 6 as a drop-in centre that it is an environment where service users feel secure, understood and under no pressure to take part in anything which they are uncomfortable with. At the same time, Number 6 aims to provide service users with the opportunity to get involved with research if they are interested in doing so. Therefore, whilst Number 6 is happy to help facilitate research into ASD, no studies will be directly endorsed by Number 6 or any Number 6 staff. In terms of facilitation, Number 6 has produced the following guidelines, based on approaches that have proved successful previously from the point of view of both Number 6 and the researcher and which have been developed with the specific social and communication issues of autism in mind. Not only have these maintained the secure, pressure free environment Number 6 works hard to create, but they have also resulted in successful recruitment of a reasonably sized subject group, motivated to take part in research.

Advertising your study

Getting Started

All proposed studies should initially be discussed with the Project Manager who will provide initial documentation (Research Questionnaire) and a brief outline of the service ethos. Once the paperwork has been completed the researcher will be asked to discuss their project with the Number 6 team. This ensures the team can answer service users queries regarding the project and also provide the researcher with relevant information about the service users.

The following guidelines are based on what has proved to be a successful model however it can be amended to suit the scope, magnitude and physical location of the project.

Become a volunteer

Attending Number 6 social events makes you a familiar face to both service users and staff. Joining a volunteer training session is also a useful way to get to know staff and become familiar with the general ethos of Number 6. (These are organised by the Volunteer Coordinator as is the Disclosure Scotland check required by Number 6 before you can become a volunteer.)

Small informal presentation

When established as someone service users are comfortable around and to talk to, the study should be introduced with a short, informal (computer) presentation to small groups of service users. Provision of a written information sheet (as requested for Ethical Approval) can be given to potential study participants at this point.

Sign-up sheet

A sign-up sheet on the notice board has also proved a useful way of letting less regular service users note their interest in the study. Number 6 staff are happy to provide contact details of any service users who have expressed an interest in the study.

Word of mouth

Many service users have expressed an interest in taking part once the study is underway and they've had a chance to discuss it with people who have already taken part. Continuing to attend some social events at Number 6 is a good way of making yourself accessible to more potential study participants and also provides opportunities to talk informally about the study with service users.

(The Number 6 newsletter is not currently used to recruit volunteers to research studies as it is used to advertise Number 6 events to service users. Including information on research studies within this letter may suggest that the research is a Number 6 event. This may be reviewed at a later date.)

Providing information on your study

Presentation

In order to ensure that service users understand what taking part involves, a short, clear, visual presentation (e.g. short PowerPoint presentation) has proven successful. It should cover who is carrying out this study, broadly speaking why the research is warranted, and a very clear explanation of the practicalities of taking part. It should also inform service users that they can leave the study at any stage. The Number 6 team are happy to give advice. (See example presentation.)

Info pack

Written material explaining the study, including an example consent form, that service users can take away and look over is also useful (such as that requested for Ethical Approval). Again, the Number 6 team are happy to be consulted on the content and level of information. (See example provided.)

Attending drop-ins

Being available to answer questions and discuss the study in an informal setting at Number 6 drop-in times has been another way to ensure that service users have every opportunity to be fully informed about what the study entails.

A combination of the above methods have been required to allow Number 6 and the researcher to feel confident that study participants are giving **fully informed** consent to take part in the study, as requested by LREC.

Practicalities

Room booking

Depending on the time and space requirements, it may be possible to carry out your research on the Number 6 premises. This has the benefit of being somewhere that service users feel safe and relaxed and can easily get to. Bookings are made through the Administrative Assistant subject to availability.

Contacting service users

Many service users have preferable means of contact, with several finding phone conversations particularly stressful. When a service user expressed an interest in taking part, their preferred method of contact was established. For the majority, organising a time to take part and asking questions about the study was most effectively done in person – again emphasising the benefits of attending Number 6 events regularly.

Coping with taking part

The nature of the study should be discussed with the Number 6 team in terms of the demands of time and concentration required by study participants. Running through the protocol with members of the team has proved useful in identifying possible distractions and sources of potential anxiety. Similarly, liaising with the Number 6 team about which service users have agreed to take part can help identify any potential issues in regard to specific individuals. Regular breaks for study participants may be required and scheduled in to the study protocol if necessary. If the study is taking place in Number 6 please be aware that there are designated areas within Number 6 which should be used if study participants need to take a break.

Feedback

What participants can expect to find out

It has been important to make clear what form of feedback will be available to study participants from the start of the study. For instance, for a group study, it was made clear that individualised feedback would not be available or in fact informative in its own right. Also, whilst questions about the sorts of tests within the study were answered honestly, explicit reference to tests such as IQ or diagnostic assessments were avoided due to the potentially contentious issues surrounding them. Whilst many participants were interested in what the different tasks and activities were trying to find out about them, all understood that during data collection, the researcher needed to make sure that how participants went about the tasks wasn't biased or influenced by what they thought the aim of the task was.

It is important to our service users that their participation is valued and they can see that they have helped contribute to something. Therefore, feedback on the main findings of the study, described in simple terms via a short presentation at a feedback party or written material is appreciated.

What participants can expect to get out of the study?

Taking part in the study should be at no cost to the volunteer. For example, travel expenses incurred taking part in the study has been reimbursed by the researcher. However, no financial incentive for taking part should be offered due to the ethical issues surrounding this. A certificate noting the study participants contribution to the study has been well received. Also, on-going, informal feedback about the study progress has been requested by many study participants.

Other considerations

Language/terminology

Service users at Number 6 have broad ranging ideas on their own diagnosis, what it means to them, and how they chose to refer to it. Therefore it is essential that especially in group settings discussion of the study is respectful of all of these views, specifically in relation to the language used. For example, using the terms 'study participants/volunteers' and 'comparison group' is used in preference to 'subjects' and 'controls'. Similarly, discussing theories of 'deficits' and 'disorders' may be appropriate in individual conversations when initiated by service users, however if such topics arise in group situations, there are a variety of private areas in Number 6 where such conversation can be moved to.

Overlap with previous research

Whilst it is appreciated that in some instances repeating assessments of the same study volunteers is inevitable, Number 6 expects researchers to be familiar with previous studies, in order to minimise unnecessary repetition. A form detailing the study must be completed prior to the study commencing (Research Questionnaire). This prevents duplication of effort of the researcher and confusion of the service user.

Keeping recruitment pressure free

As mentioned previously, ensuring that service users feel under no pressure to take part is of paramount importance for the research to work successfully and in harmony with Number 6. The strategies which have proved successful to advertise and inform service users about the study have ensured that at some point, the service user has to initiate their own involvement. At the same time, the strategies were chosen to make this as easy and stress free as possible. The very high attendance rate for appointments (only one cancellation out of 23 which then rebooked) supports these strategies, and has meant that both

Number 6 and the researcher have felt study participants have been genuinely comfortable taking part.

In general, a service user should have a 6 month break between studies.

Contact details

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**Appendix 2 - Deficits in facial, body movement and
vocal emotional processing in autistic spectrum
disorder**

Submitted for publication in Psychological Medicine

Running title: Emotion processing in ASD

Deficits in facial, body movement and vocal emotional processing in autism spectrum disorders

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Abstract

Background: Previous behavioural and neuroimaging studies of emotion processing in Autistic Spectrum Disorder (ASD) have focussed on the use of facial stimuli. To date, however, no studies have examined emotion processing in autism across a broad range of social signals.

Methods: This study addressed this issue by investigating emotion processing in a group of 23 adults with ASD and 23 age and gender matched controls. Recognition of basic emotions ('happiness', 'sadness', 'anger', disgust' and 'fear') was assessed from facial, body movement and vocal stimuli. The ability to make social judgements (such as judgements of approachability) from facial stimuli was also investigated.

Results: Significant deficits in emotion recognition were found in the ASD group relative to the control group across all stimulus domains (faces, body movements and voices). These deficits were seen across a range of emotions. The ASD group were also impaired in making social judgements compared to the control group and this correlated with impairments in basic emotion recognition.

Conclusion: This study demonstrates that there are significant and broad ranging deficits in emotion processing in ASD present across a range of stimulus domains and in the auditory and visual modality; they cannot therefore be accounted for simply in terms of impairments in face processing or in the visual modality alone. These results identify a core deficit affecting the processing of a wide range of emotional information in ASD which contributes to the impairments in social function seen in people with this condition.

Introduction

Autism, as defined by DSM-IV criteria, is a developmental disorder characterised by difficulties in social interaction, a restricted repetitive range of interests and behaviours and impairments in verbal and non-verbal communication. There is a broad clinical phenotype, which encompasses a wide range of behaviour and degrees of global intellectual impairment. This results in a diverse clinical population, generally described as having an Autism Spectrum Disorder (ASD). Individuals on the autistic spectrum who do not show global intellectual impairment are commonly referred to as having High Functioning Autism (HFA) if they have a history of significant language delay and Asperger's Syndrome (AS) if they do not. For adults with HFA/AS it is the difficulties in social communication and interaction that are frequently the most debilitating.

Studies have identified deficits in facial emotion recognition in both children (Celani *et al.*, 1999) and adults (Adolphs *et al.*, 2001, Hobson *et al.*, 1988b, Howard *et al.*, 2000, Pelphrey *et al.*, 2002) with autism. Understanding more complex emotional and social information from facial stimuli is also thought to be impaired in autism (Baron-Cohen *et al.*, 2001a). Although the majority of studies have focused on face stimuli, there is some evidence to suggest that the abnormalities of emotion processing may also be present in other types of visual stimuli such as body movement (Hubert *et al.*, 2007, Moore *et al.*, 1997). However there is also evidence to suggest that the ability to process biological motion, regardless of whether emotional content is present or not, is impaired in autism (Blake *et al.*, 2003).

The literature to date therefore suggests that individuals with autism may be impaired in recognising emotional content in a variety of visual stimuli. It is however possible that

the apparent deficits in emotion recognition in faces and from movement derive from general impairments in the processing of visual stimuli. Investigating emotion processing in the auditory modality is one way to examine whether there is a core deficit in emotion processing in ASD: if deficits in emotional processing of faces and whole body movement result from deficits in visual processing style and/or visual attention then emotional processing in the auditory domain should be preserved. Findings from the limited literature on vocal emotion processing have however provided mixed results. Hobson et al (1988a) found that a group of adolescents with autism and co-morbid learning disability performed less well than controls when asked to match faces to emotional voices. Conversely, Loveland et al (1997) found that recognition of emotion in verbal and non-verbal stimuli was influenced by the intellectual ability of the participants, regardless of autism diagnosis. It is important to note, however, that the tasks used in both of these studies involved vocal emotional stimuli in addition to emotion displayed in a different modality (faces or gestures) and therefore did not investigate vocal emotion processing in isolation. Rutherford et al (2002) carried out the Reading the Mind in the Voice task which involves stimuli purely in the auditory domain and demonstrated deficits in autistic participants' ability to extract complex mental states from dialogue. Simple recognition of basic emotional states from vocal stimuli has been reported to be both as accurate as controls (O'Connor, 2007) and impaired (Mazefsky and Oswald, 2007).

In the current study we sought to investigate whether individuals with ASD have pervasive deficits in emotion processing across stimulus domains. The perception of a range of social signals was examined using tasks of comparable format to investigate face, body movement and voice emotion processing in a group of subjects with ASD and

age and gender matched controls. We also extended our investigation into social cognition judgements as associated with facial stimuli in ASD.

We had three main hypotheses: firstly that the ASD group would show deficits in emotion processing across a range of stimulus modalities; secondly, that these deficits would extend across a range of emotional states and thirdly, that subjects with ASD would also show related impairments in making social judgements.

Methods

Participant details

23 individuals with ASD were recruited from 'Number 6', a drop-in centre and service provider for adults with AS or HFA in Edinburgh and the Lothians (www.number6.org.uk), with close links to the regional ASD health service. The ASD subject group had a mean age of 32.5 years (s.d. 10.9 years) and consisted of 16 males and 7 females. Participants were excluded from the ASD group if they had a diagnosed co-morbid psychiatric disorder. The control group was matched by age [mean age 32.4 years (s.d. 11.1 years)] and gender (17 male, 6 female) and consisted of typically developing volunteers who reported no personal or family history (first degree relative) of ASD or a major psychiatric disorder. All study volunteers provided informed consent and the study was approved by the Local Research Ethics Committee.

Test Procedures

Diagnostic measures of ASD

All members of the ASD group had previously received a diagnosis of an ASD through multidisciplinary assessment by clinical services in South-East Scotland. DSM-IV

diagnostic categories were confirmed through a combination of case note review and assessment by a clinician experienced in the diagnosis of autism spectrum disorders in adults (AS).

To further characterize the current level of autistic behaviour, ASD participants completed the Autism Diagnostic Observational Schedule (ADOS) (Lord et al., 2000), the Autism Quotient (AQ) (Baron-Cohen *et al.*, 2001b), Empathy Quotient (EQ) (Baron-Cohen and Wheelwright, 2004) and Systemising Quotient (SQ) (Baron-Cohen et al., 2003).

Background measures of cognitive ability

Intelligence quotient (IQ) scores were obtained using the Wechsler Abbreviated Scale of Intelligence (WASI). The Benton Test of Facial Recognition (Benton et al., 1983) was employed to establish basic face processing ability.

Emotion recognition

Emotion processing ability was investigated across three stimulus domains; faces, body movement and voices.

a) Face tasks

A range of tasks was employed to investigate facial emotion processing. The first task was the Ekman 60 Faces Test from the FEEST (Young et al., 2002) in which participants have to select a textual label to describe the emotion expressed in a face presented to them on a computer monitor. The stimuli were selected from Ekman and Friesen's (1976) pictures of facial affect series. Each face stimulus was presented for 5 seconds and participants had a choice of six emotion labels: 'happiness', 'sadness', 'anger',

'disgust', 'fear' and 'surprise'. Ten trials for each emotion were presented in random order and participants received no feedback on task performance. The second task was the Emotion Hexagon task from the FEEST (Young et al., 2002) which employs the same task structure but stimuli are computer-morphed to differ in the extent to which they express the emotion, thus providing a more sensitive measure of emotion labelling ability.

A further two tasks of facial emotion processing were developed, both using stimuli from the JACFEE series (Matsumoto and Ekman, 1988). In the first Face Emotion Label task, participants were again presented with a face on the computer monitor for 5 seconds. This time, they had only five textual labels to choose from as 'surprise' was omitted to allow a more direct comparison between tasks involving facial emotion and those involving emotion in voices and body movements, for which 'surprise' stimuli were not available (Murray and Arnott, 1993). There were seven trials for each emotion and the 35 stimuli were presented in random order. The second task to employ the JACFEE stimuli was a Face Emotion Match task. Participants were required to match the target stimuli to another picture of a face according to the emotional expression. Again, they had a choice of five as 'surprise' was omitted, and there were 7 trials for each emotion presented in random order on the computer monitor. This task was included as it has no verbal labeling component.

b) Body movement task

In the Body Movement Emotion Label task participants were required to select a text label from a choice of five ('happiness', 'sadness', 'anger', 'disgust' and 'fear') to describe the emotion expressed in a short movie clip. The movies ranged from 5 – 10 seconds and consisted of individual male and female actors depicting one of five

emotions with whole-body movements. No facial emotion was visible. Ten trials of each emotion were presented in random order and responses received no feedback. The whole-body movement stimuli depicting basic emotions in full light is part of a standardised stimulus set from Atkinson et al (2004).

c) Voice task

In the Voice Emotion Label task, participants were required to select a text label from a choice of five ('happiness', 'sadness', 'anger', 'disgust' and 'fear') to describe the emotion in vocal stimuli. Calder Vocal Emotion stimuli were used which last 5 – 10 seconds and consist of male and female actors saying strings of numbers in an emotional tone (Calder et al., 2004). Ten trials of each emotion were presented in random order and responses received no feedback.

Tests of Social Judgement

A final set of tasks tested ability to make a range of social judgements from faces. A full description of the derivation of this set of tasks is available elsewhere (Hall *et al.*, 2004, Santos, 2003, Santos and Young, 2008). Briefly, a database of one thousand pictures of faces of non-famous adults were acquired from media sources and were rated by six volunteer participants on six social dimensions (age, trustworthiness, intelligence, attractiveness, approachability and distinctiveness) using 1 to 7 point scales. A mean rating for each characteristic was then computed for each facial stimulus. For each characteristic, 40 faces were then selected comprising 20 faces representative of high and 20 faces of low valence to construct the final task. Each individual face appeared only in one set; completely different faces were selected for the sets of faces involving judgments of age, attractiveness, etc. The sets of faces for each social dimension were

matched as closely as possible on the remaining five dimensions and half the stimuli were male and half female.

In the present study participants were shown 40 faces (8 practice and 32 test images) for each of the six social characteristics on a computer monitor. Each stimulus was presented for 5 seconds. Participants were asked via text prompts to make a two-alternative forced-choice judgement on the face relating to age (old or young) in set 1, trustworthiness (very trustworthy or not trustworthy) in set 2, attractiveness (attractive or unattractive) in set 3, intelligence (very intelligent or not intelligent) in set 4, approachability (very approachable or not approachable) in set 5 and distinctiveness (very distinctive or not distinctive) in set 6. A response was considered an error whenever it did not correspond to the categorisation of the stimulus derived from the independent ratings (Hall *et al.*, 2004, Santos, 2003, Santos and Young, 2008).

Statistical analysis

Statistical analysis was carried out in SPSS, version 14.0 for Windows. T-tests were used to investigate mean differences between the ASD and control groups in the AQ, EQ and SQ, measures of IQ and performance on the Benton Face Recognition Task.

Separate repeated measures Analyses of Variance (ANOVA) were employed for each task of emotion recognition and the social judgment task with emotion/judgment as the within subject variable and group as the between subject factor. Following the investigation of effects of group, effects of emotion and group x emotion interactions, the effect of group was investigated for each emotion separately using independent t-tests. Standard residuals were examined to check that data were normally distributed before parametric statistical tests were applied.

To illustrate the pattern of errors made by the control group and ASD group in the Face Emotion Label task, the Body Movement Emotion Label task and the Voice Emotion Label task confusion matrices were constructed by calculating the number of times each emotion was given in response to a stimulus.

As significant group differences were found in relation to IQ scores and performance of the Benton Face Recognition Test, the original analysis was repeated on subsets of the study population, matched on these measures. Exploratory analyses to test for group x gender interactions were also carried out for each emotion. Furthermore, due to the range of symptom severity present in the ASD sample, an exploratory analysis was carried out with the ASD group sub-divided according to the level of behavioural symptoms observed using the ADOS.

Pearson's correlation was used to investigate associations between task performances across modalities in the emotion label tasks and the relationship between basic emotion label ability and social cognition.

Results

Diagnostic assessment

All participants within the subject group met DSM-IV criteria for ASD. The ASD group scored significantly higher on each sub-set of the AQ compared to the control group ($p < 0.001$, see table 1) and significantly lower on the Empathising Quotient ($p < 0.001$). However there was no significant difference between groups on scores for the

Systemising Quotient (see table 1). Despite the positive clinical diagnoses, only 11/23 participants scored above the ADOS cut-off.

Background measures of cognitive abilities

Verbal and full scale IQ scores (VIQ and FSIQ) were lower in the ASD group than in the control group. There was no significant difference in performance IQ scores (PIQ) between the groups (see table 1). For scores on the Benton Test of Facial Recognition the control group mean was 46 (s.d. 2.8), with a range of 41-52; all group members scoring in the non-impaired range. The mean ASD group score was 43.35 (s.d. 4.39), range 36-50. Whilst the mean score is within normal limits 4 members of the ASD group scored below 39 indicating a face recognition impairment (Benton et al., 1983). The difference between mean group scores was statistically significant ($p=0.02$).

Emotion recognition

Faces

Data for the 4 facial emotion tasks are presented in supplementary table1. In the Ekman 60 Faces task there was a significant effect of group [$F(1,46)=27.7$, $p<0.001$], a significant effect of emotion [$F(5,46)=17.12$, $p<0.001$] and a significant group x emotion interaction [$F(5,46)=2.96$, $p=0.013$]. Post-hoc t-tests demonstrated that the ASD group performed significantly worse in the Ekman 60 Faces task across all six emotions ($p<0.05$), with the greatest impairment being apparent in 'anger'.

In the Emotion Hexagon task, again there was a significant effect of group [$F(1,46)=17.46$, $p<0.001$], a significant effect of emotion [$F(5,46)=11.41$, $p<0.001$] and a significant group x emotion interaction [$F(5,46)=2.41$, $p=0.037$]. ASD group performance was poorer across all emotions in the Emotion Hexagon task. This reached statistical

significance for 'anger', 'sadness', 'fear' and 'surprise' ($p < 0.05$) with the greatest deficits seen in 'anger' and 'fear'. Difference in performance in labelling 'disgust' reached trend level ($p = 0.059$).

In the Face Emotion Label task the ASD group performed worse than the control group across all emotions (figure 1A). There was a significant effect of group [$F(1,46) = 9.3$, $p = 0.004$], a significant effect of emotion [$F(4,46) = 10.69$, $p < 0.001$] and a significant group x emotion interaction [$F(4,46) = 3.17$, $p = 0.015$]. The difference in group performance was then investigated for each emotion separately and found to be statistically significant for 'sadness', 'anger' and 'disgust'. In the Face Emotion Match task, there was a significant effect of group [$F(1,46) = 10.1$, $p = 0.003$], a significant effect of emotion [$F(4,46) = 10.09$, $p < 0.001$] and a significant group x emotion interaction [$F(4,46) = 2.69$, $p = 0.033$]. Statistically significant differences between the ASD and control group were found for 'sadness', 'anger' and 'disgust'.

Body movement

There was a significant effect of group [$F(1,46) = 17.42$, $p < 0.001$] and a significant effect of emotion [$F(4,46) = 18.82$, $p < 0.001$] in the Body Movement Label task, however there was no significant group x emotion interaction [$F(4,46) = 1.44$, $p = 0.222$]. The ASD group was less accurate in identifying emotion from body movement for all emotions, with the greatest deficits being present in 'happiness' and 'fear' (see figure 1B and supplementary table 1).

Voices

In the Voice Emotion Label task, there was a significant effect of group [$F(1,46) = 25.46$, $p < 0.001$], a significant effect of emotion [$F(4,46) = 5.53$, $p < 0.001$] and a significant group

x emotion interaction [$F(4,46)=2.89$, $p=0.024$]. The ASD group again scored lower than the control group across all five emotions, with the greatest deficits found in 'anger' and 'disgust' (see figure 1C and supplementary table 1).

Error patterns in basic emotion labelling tasks

The pattern of errors in each task for each group is illustrated in the confusion matrices (table 2). These data demonstrate that the number and type of errors made vary according to modality, with the deficits in emotion labeling performance seen in the ASD group resulting from increased numbers of similar errors made by the control group.

Social Cognition

In the tasks of social cognition, there was a significant effect of group [$F(1,46)=17.48$, $p<0.001$], a significant effect of emotion [$F(5,46)=27.97$, $p<0.001$] and a significant group x judgement interaction [$F(5,46)=5.2$, $p<0.001$]. Further exploration with post-hoc t-tests identified deficits in the ASD group when making judgements of approachability, attractiveness, intelligence, and distinctiveness. The difference in mean score for these attributes reached statistical significance ($p=0.001$ for approachability, attractiveness, and distinctiveness, $p=0.005$ for intelligence) (figure 2A and supplementary table 1).

Correlation of task performance across modalities and in relation to social cognition ability

As presented in figure 1D, E and F, in the ASD group performance on each emotion labelling task was significantly and positively correlated with emotion labelling ability in the other two stimulus domains. Face Emotion Label performance correlated with Voice Emotion Label performance (Pearsons $r=0.646$, $p=0.001$) and Body Movement Emotion Label performance (Pearsons $r=0.701$, $p<0.001$). Voice Emotion Label performance

also correlated with performance in the Body Movement Emotion Label task (Pearsons $r=0.665$, $p=0.001$). The total emotion labelling score, an average score taken from each of the basic emotion label tasks, correlated with the average social cognition score in the ASD group (Pearsons $r=0.48$, $p=0.021$, figure 2B).

Analysis of task performance by ADOS score

Despite all having a clinical diagnosis of ASD, around half of our sample did not meet criteria for an ADOS categorisation of ASD. An exploratory analysis was therefore carried out to examine task performance with the ASD group sub-divided according to whether or not participants scored above cut-off on the ADOS (see table 3). This analysis revealed that both groups showed impairments relative to the control group, with the task performance of those scoring below the ADOS cut-off lying intermediate between the performance of those who scored above the cut-off and the controls.

Effects of possible confounds

The ASD group have a significantly lower full scale IQ (FSIQ) score than the control group ($p=0.029$) therefore a sub-set of participants ($n=17$ in each group) with matched IQ were selected and the original analysis repeated; repeated measures ANOVAs revealed a similar pattern of results to those seen in the full group (see supplementary table 2).

Similarly, as scores of the Benton Task of Face Recognition differ significantly between groups, ASD participants who had a Benton score indicative of face recognition impairment were excluded and the analysis of emotion and social tasks involving the face stimuli were repeated. When groups were matched for Benton task performance, the original pattern of results remained, suggesting that deficits in face recognition do not

account for the emotion processing impairments presented in this study (see supplementary table 3).

As the gender ratio in this ASD population (16:7) is somewhat higher than what is seen typically (4:1), the effect of gender was investigated; there was no significant gender x group interaction in any of the emotion or social cognition tasks.

Discussion

We have demonstrated that people with ASD have significant impairments in emotion recognition across a range of stimulus domains and both the visual and auditory modalities. These results cannot be accounted for in terms of a failure to process emotional information in any single stimulus domain or sensory modality and therefore strongly support the view that ASD involves a generalised impairment in emotion recognition. The same participants also had impairments in making other social judgements, suggesting that the deficits seen in emotion recognition could be part of a broader deficit in mental state attribution. Notably the deficits in emotion recognition correlated with the deficits in social judgement. The emotion and social processing impairments observed in the ASD group could not be accounted for by any differences in IQ or basic face processing ability between groups.

Cross modal deficits

The deficits displayed by the ASD group in each emotion processing task strongly support our hypothesis of cross-modal emotion processing deficits. Our findings of deficits in facial emotion processing across a range of tasks are in line with earlier studies (Adolphs *et al.*, 2001, Celani *et al.*, 1999, Howard *et al.*, 2000, Pelphrey *et al.*,

2002). Previous reports (reviewed by (Sasson, 2006)) and indeed our own data from the Benton Task of Facial Recognition, suggest that basic face processing, regardless of emotion, may be impaired in ASD. However, differences were still apparent when the groups in the current study were matched for Benton task performance suggesting that the results are not accounted for by deficits in basic face processing.

Deficits in the task of emotion recognition from body movement replicate previous findings (Blake *et al.*, 2003, Hubert *et al.*, 2007) reinforcing the view that processing emotion from whole-body movement is also deficient in ASD. However the deficits in our ASD group appear less marked than those reported by Hubert et al (2007). This could be accounted for by the difference in demands in the body movement emotion label task applied here which used full body images as opposed to point light displays allowing a) full view of the body and b) low motion coherence requirements when depicting whole-body movement stimuli. Furthermore, in the Hubert study (2007) participants were asked to spontaneously generate descriptive language whereas our task provided a limited number of textual options with which to respond.

We also demonstrated deficits in vocal emotion processing in the ASD group compared to the control group. This is in contrast to the findings of O'Connor (2007) who reported equivalent recognition of emotion from auditory stimuli in the ASD group relative to control group performance. Variations in task design may account for the difference in results between the studies. Firstly, the task used in this study provides participants with five options with which to respond; in the O'Connor study only three emotions were investigated. Secondly, in the O'Connor study, participants labelled auditory stimuli which they had already been exposed to in a previous emotion processing task which

may have conferred an advantage. Our data indicates that deficits in emotion processing in autism also extend to the auditory modality.

Whilst the vast majority of previous emotion processing studies in ASD have utilised static facial representations of emotion (Adolphs *et al.*, 2001, Ashwin *et al.*, 2007b, Critchley *et al.*, 2000, Dalton *et al.*, 2005, Deeley *et al.*, 2007, Hall *et al.*, 2003, Howard *et al.*, 2000, Koshino *et al.*, 2007, Ogai *et al.*, 2003, Pelphrey *et al.*, 2002, Piggot *et al.*, 2004, Wang *et al.*, 2004) we show here that deficits in emotion recognition are not isolated to this type of stimulus. This broad ranging deficit in emotion recognition is therefore unlikely to be accounted for by processing demands or a processing style adopted for any specific stimulus domain. Differences in eye gaze pattern whilst processing static face stimuli (Dalton *et al.*, 2005, Klin *et al.*, 2002, Pelphrey *et al.*, 2002, Spezio *et al.*, 2007), for example, cannot account for the observed deficits in identifying emotion in body movement and voice stimuli. Although we did not specifically monitor eye-gaze during our visual experiments, the cross-modal impairments in the ASD group reported here which include deficits in auditory emotion processing could not be fully accounted for by atypical scan paths during face processing.

Cross-emotion deficits

Whilst previous studies (Howard *et al.*, 2000, Pelphrey *et al.*, 2002) demonstrated a differentially severe deficit in the identification of the emotion of fear from faces we report a broader deficit in emotion recognition. Each of the basic emotions tested was impaired in at least one domain lending further weight to the idea of a global deficit in emotion processing in ASD. This suggests that impairments in emotion recognition in ASD lie in a substrate common to the processing of a wide range of emotional states.

Social judgement deficits

The deficits in the ASD group extended to the tasks of social cognition in support of our third hypothesis. These tasks assess participants' ability to make social judgements from a static facial image. Our finding of deficits in a range of decisions extends previous work which was limited to decisions relating to 'trustworthiness' and 'approachability' (Adolphs et al., 2001). Whilst we replicated Adolphs et al (2001) finding of differences in judging approachability, the ASD group studied here were equivalent to the control group in their judgements of trustworthiness. Differences in the format of the task used may account for this; Adolphs et al (2001) provide a scale with which participants rate trustworthiness whereas in this study participants were asked to make a dichotomous decision. The overall poorer task performance in these social tasks however supports the notion of a generalised dysfunction in processing social information from human stimuli in autism as reported previously in studies assessing mentalizing ability (Baron-Cohen *et al.*, 1997, Baron-Cohen *et al.*, 1999, Castelli *et al.*, 2002, Frith, 2001, Happé *et al.*, 1996). The significant positive correlation between ASD participants' performance of simple emotion recognition and these social judgements provides evidence that basic emotion processing skills are predictive of more general social ability.

Study limitations

It is important to note that, whilst all members of the ASD group had received a clinical diagnosis through multidisciplinary assessment by clinical services, only half of the group demonstrated sufficient current behavioural symptoms to score above the cut off on the ADOS. Notably, all of the participants who did not meet criteria on the ADOS had clinical diagnoses of either Asperger syndrome or PDD-NOS, rather than autistic disorder. Although it is possible that the clinical diagnostic process may be over-

inclusive, the findings when the group were sub-divided by ADOS score suggest this is not the case, with cross-modal deficits in emotion processing present in both groups. Interestingly, those scoring below the cut-off, although still impaired, showed less marked deficits in emotion processing than those who scored above the cut-off. This may indicate that while those below the cut-off are indeed correctly classified as being on the autism spectrum they are less severely affected than those above the cut-off.

Other potential limitations to the current study include the lack of a standardised parental interview, such as the Autism Diagnostic Interview. Although parental interviews had been conducted for the majority of individuals during the original clinical diagnostic evaluation, we did not repeat this process as participants were adults recruited directly from a voluntary sector service. Furthermore, it should be noted that all ASD participants were individuals who chose to access a voluntary sector service therefore the population studied may not necessarily be representative of the general autistic population.

Despite these limitations, the present study demonstrates robust findings of cross modal emotion processing deficits in a clinically diagnosed sample with ASD. These findings suggest that previously reported deficits in emotion processing in ASD are not limited to one particular modality and are therefore likely to represent a core deficit in emotion processing, with consequentially impacts on social function.

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Emotion Processing in Autism Spectrum Disorder

	ASD group mean(sd) (range)	Control group mean(sd) (range)	p-value
Autism Quotient (n=23, 23)			
Social skill	6.87 (2.62)	0.96 (1.19)	<0.001
Attention switching	8.26 (1.51)	3.65 (2.27)	<0.001
Attention to detail	6.70 (2.12)	4.83 (2.27)	0.006
Communication	6.70 (1.82)	1.74 (1.54)	<0.001
Imagination	5.87 (2.32)	1.96 (1.40)	<0.001
AQ total	34.39 (7.65) (21-46)	13.13 (5.46) (6-29)	<0.001
Scores > 26	19/23	1/19	
Empathy Quotient (n=20, 21)	33.45 (8.36) (21-52)	52.10 (15.44) (16-72)	<0.001
Systemising Quotient (n=18, 21)	27.61 (14.60) (4-66)	30.76 (12.97) (12-64)	0.484
Test of IQ			
WASI VIQ	98.2 (15.8) (64-123)	106.8 (8.8) (86-120)	0.029
WASI PIQ	104.4 (18.6) (63-134)	113.4 (10.4) (96-129)	0.052
WASI FSIQ	101.5 (18.5) (60-126)	111.2 (8.5) (94-124)	0.029

Table 1 – Mean group scores with standard deviations and ranges for Autism, Empathy and Systemising Quotients and tests of IQ. T-tests were applied to compare group means; p-values are displayed.

Emotion Processing in Autism Spectrum Disorder

Control Group Confusion Matrix for Face Emotion Label Task						ASD Group Confusion Matrix for Face Emotion Label Task					
	Response						response				
	Anger	disgust	fear	Happiness	sadness	emotion	anger	Disgust	fear	happiness	sadness
Anger	0.85	0.12	0.01	0.00	0.02	anger	0.65	0.25	0.04	0.00	0.06
Disgust	0.07	0.91	0.02	0.00	0.00	disgust	0.16	0.73	0.06	0.02	0.03
fear	0.01	0.12	0.87	0.00	0.01	fear	0.03	0.09	0.84	0.01	0.03
happiness	0.00	0.00	0.00	1.00	0.00	happiness	0.00	0.02	0.00	0.98	0.00
sadness	0.00	0.01	0.04	0.00	0.95	sadness	0.01	0.08	0.05	0.01	0.85

Control Group Confusion Matrix for Body Movement Emotion Label Task						ASD Group Confusion Matrix for Body Movement Emotion Label Task					
	Response						response				
	Anger	disgust	fear	Happiness	sadness	emotion	anger	Disgust	fear	happiness	sadness
Anger	0.90	0.08	0.00	0.01	0.01	anger	0.77	0.15	0.02	0.03	0.04
Disgust	0.02	0.74	0.14	0.04	0.06	disgust	0.09	0.51	0.17	0.03	0.20
fear	0.00	0.05	0.93	0.00	0.01	fear	0.04	0.06	0.81	0.02	0.07
happiness	0.07	0.01	0.01	0.90	0.00	happiness	0.20	0.04	0.01	0.74	0.00
sadness	0.00	0.03	0.11	0.00	0.85	sadness	0.03	0.04	0.18	0.00	0.75

Control Group Confusion Matrix for Voice Emotion Label Task						ASD Group Confusion Matrix for Voice Emotion Label Task					
	Response						Response				
	Anger	disgust	fear	Happiness	sadness	emotion	anger	Disgust	fear	happiness	Sadness
Anger	0.83	0.08	0.00	0.07	0.01	anger	0.59	0.22	0.04	0.11	0.04
Disgust	0.08	0.77	0.04	0.04	0.07	disgust	0.12	0.46	0.12	0.14	0.16
fear	0.01	0.03	0.80	0.08	0.09	fear	0.05	0.07	0.58	0.18	0.12
happiness	0.02	0.07	0.07	0.77	0.07	happiness	0.02	0.11	0.16	0.56	0.16
sadness	0.01	0.14	0.04	0.01	0.81	sadness	0.02	0.08	0.09	0.05	0.76

Table 2 – Confusion matrices for the control and ASD groups for the Face, Body Movement and Voice Emotion Label tasks.

Emotion Processing in Autism Spectrum Disorder

Basic Emotion Processing Task Performance						
Task	Control group accuracy (%)	sd	ADOS -ve ASD group accuracy (%)	sd	ADOS +ve ASD group accuracy (%)	sd
Ekman60	88.30	5.47	73.83	14.56	67.36	14.98
Ekman Hexagon	92.43	7.57	81.33	13.53	76.45	14.00
Face Emotion Match	93.09	9.48	84.50	10.67	82.64	11.52
Face Emotion Label	91.83	9.57	84.00	17.67	74.82	14.70
Body Movement Emotion Label	86.17	7.18	72.67	18.32	70.18	11.88
Voice Emotion Label	78.96	8.46	62.83	16.72	58.73	13.24

Table 3 – Task performance accuracy (totals across all emotions) for all emotion processing tasks for the control group and the ASD group subdivided according to ADOS score. Control group; n=23, age=32.4 (11.1), ASQ=13.1 (5.4), FSIQ=111.2 (8.5). ADOS –ve ASD group; n=12, age=31.5 (11.2), ASQ=35.2 (7.8), FSIQ=105.3 (13.5). ADOS +ve ASD group; n=11, age=33.7 (11), ASQ=33.5 (7.7), FSIQ=97.4 (22.8).

Supplementary tables

Ekman 60

Emotion	ASD group accuracy (%)	sd	Control group accuracy (%)	sd	p-value
Happiness	94.78	11.63	100.00	0.00	0.043
Sadness	65.65	24.09	82.61	14.21	0.006
Anger	61.30	25.99	90.43	7.06	<0.001
Disgust	65.65	27.44	84.78	17.29	0.007
Fear	58.26	26.05	80.87	16.49	0.001
Surprise	79.57	22.66	90.87	9.96	0.036
Total	70.74	14.79	88.30	5.47	<0.001

Ekman Hexagon

Emotion	ASD group accuracy (%)	sd	Control group accuracy (%)	sd	p-value
Happiness	96.52	5.73	98.26	4.16	0.246
Sadness	83.70	18.42	97.39	5.41	0.002
Anger	72.83	20.72	91.74	14.35	0.001
Disgust	68.91	30.82	84.35	22.27	0.059
Fear	69.78	26.44	91.09	12.88	0.001
Surprise	81.30	17.20	92.17	9.75	0.012
Total	79.00	13.67	92.43	7.57	<0.001

Face Emotion Match

Emotion	ASD group accuracy (%)	sd	Control group accuracy (%)	sd	p-value
Happiness	96.91	7.42	96.91	14.80	1.000
Sadness	77.04	23.16	94.43	11.20	0.003
Anger	85.65	17.84	95.09	8.15	0.028
Disgust	72.70	21.50	86.35	20.40	0.032
Fear	85.78	14.97	93.17	10.51	0.059
Total	83.61	10.87	93.09	9.48	0.003

Face Emotion Label

Emotion	ASD group accuracy (%)	sd	Control group accuracy (%)	sd	p-value
Happiness	98.17	4.82	100.00	0.00	0.083
Sadness	83.30	26.08	95.04	13.34	0.063
Anger	62.17	34.14	88.17	13.51	0.002
Disgust	72.09	29.39	89.48	18.85	0.022
Fear	82.65	23.12	86.96	26.25	0.558
Total	79.61	16.62	91.83	9.57	0.004

Body Movement Emotion Label

Emotion	ASD group accuracy (%)	sd	Control group accuracy (%)	sd	p-value
Happiness	72.61	16.85	89.13	7.93	<0.001
Sadness	76.52	20.80	85.22	15.34	0.114
Anger	77.39	19.82	89.13	12.40	0.021
Disgust	51.74	30.40	73.91	17.77	0.005
Fear	79.13	15.93	93.48	5.73	<0.001
Total	71.48	15.28	86.17	7.18	<0.001

Emotion Processing in Autism Spectrum Disorder

Voice Emotion Label					
Emotion	ASD group accuracy (%)	sd	Control group accuracy (%)	sd	p-value
Happiness	57.83	20.66	76.96	14.60	0.001
Sadness	75.22	15.34	80.00	14.14	0.278
Anger	63.48	20.14	83.48	14.96	<0.001
Disgust	48.26	30.55	76.52	17.48	<0.001
Fear	59.57	25.85	77.83	11.66	0.004
Total	60.87	14.96	78.96	8.46	<0.001

Social Cognition Decision					
Judgement	ASD group accuracy (%)	sd	Control group accuracy (%)	sd	p-value
Age	94.87	4.98	95.74	7.14	0.634
Trustworthiness	81.35	9.44	80.83	9.67	0.854
Intelligence	77.83	10.49	86.74	9.96	0.005
Approachability	79.61	16.60	93.13	6.19	0.001
Attractiveness	78.57	11.12	88.30	7.93	0.001
Distinctiveness	67.35	14.99	80.48	8.66	0.001

Supplementary table 1 – Task performance accuracy for all emotion and social tasks for the ASD and control groups. P-values for post hoc t-tests are also displayed.

IQ matched sub groups

Task	emotion*group		effect of emotion		effect of group	
	F	p	F	P	F	P
Ekman60	2.923	0.015	13.649	<0.001	14.194	0.001
Ekman Hexagon	2.064	0.073	7.666	<0.001	10.096	0.003
Face Emotion Match	1.823	0.128	7.832	<0.001	4.582	0.04
Face Emotion Label	2.079	0.087	9.231	<0.001	4.09	0.052
Voice Emotion Label	2.096	0.085	3.557	0.009	10.213	0.003
Body Movement Emotion Label	1.053	0.383	12.804	<0.001	10.469	0.003
Social Cognition Task	2.406	0.039	20.668	<0.001	11.15	0.002

Supplementary table 2 – Results of repeated measures ANOVA performed on subsets of the ASD and control groups. Control group; n=17, 12 male, age=29.7 (6.5), FSIQ=111 (9.1). ASD group; n=17, 12 male, age=33.5 (11.6), FSIQ=110.2 (11). T-tests revealed no significant differences between groups on age or FSIQ.

Analysis with ASD participants with impairment in face recognition (as indicated by scores on the Benton Task of Facial Recognition) excluded

Task	emotion*group		effect of emotion		effect of group	
	F	P	F	P	F	P
Ekman60	8.14	0.007	12.66	0.001	20.38	<0.001
Ekman Hexagon	2.54	0.119	13.997	0.001	12.566	0.001
Face Emotion Match	13.176	0.001	17.768	<0.001	6.820	0.013
Face Emotion Label	6.858	0.012	14.612	<0.001	5.720	0.022
Social Cognition Task	31.194	<0.001	108.748	<0.001	15.359	<0.001

Supplementary table 3 – Results of repeated measures ANOVA with ASD participants with face recognition impairment excluded. Control group; n=23, 17 male, age=32.4 (11.1), Benton score=46 (2.8). ASD group; n=19, 15 male, age=33.2 (11.6), Benton score=44.7 (3.4). T-tests revealed no significant differences between groups on age or Benton score.

Emotion Processing in Autism Spectrum Disorder

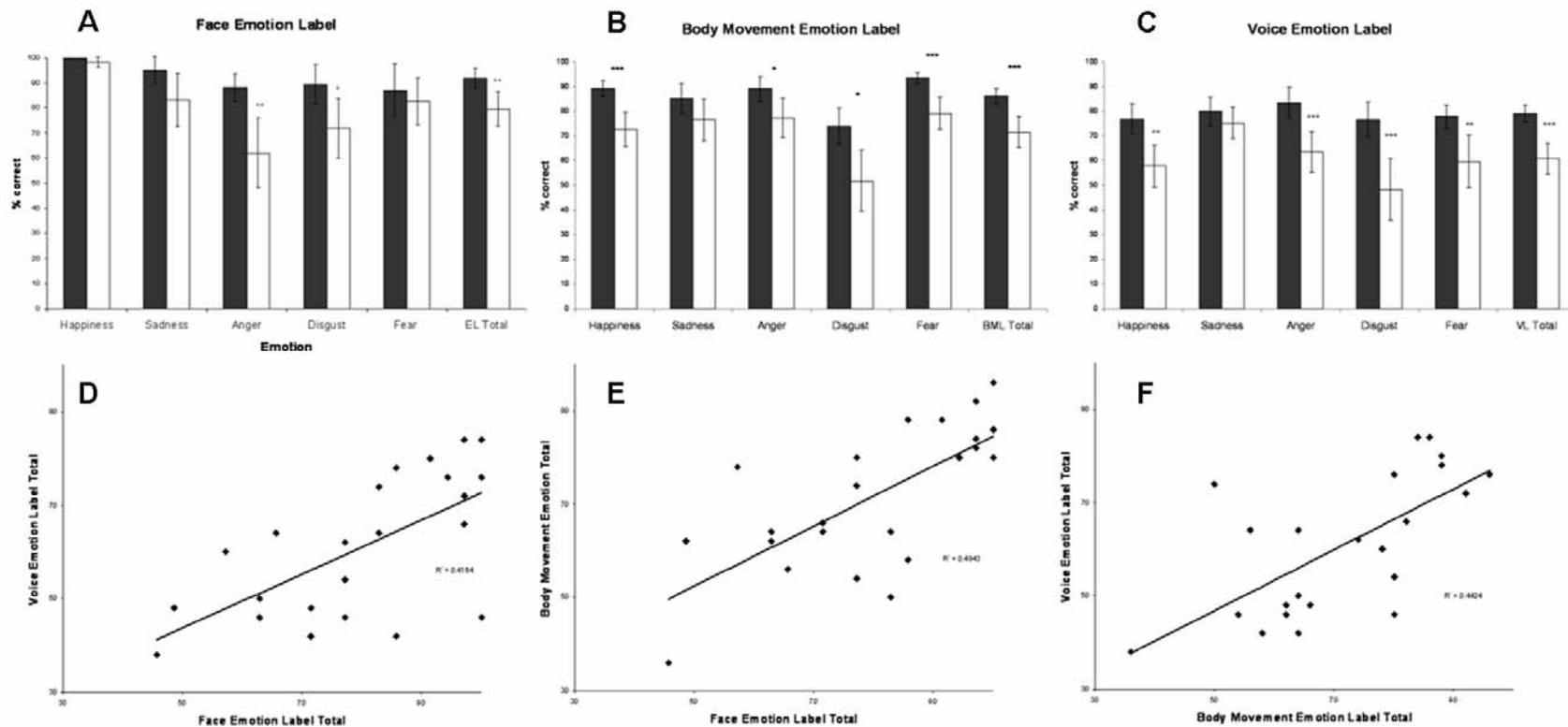


Figure 1 – Percentage of correct responses for A) the Face Emotion Label task, B) the Body Movement Emotion Label task and C) the Voice Emotion Label task. Control group mean is in black, ASD group mean is in white. 95% confidence intervals are displayed. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$. Correlations between performance in each of the emotion label tasks in the ASD group, D) vocal emotion vs facial emotion, E) body movement emotion vs facial emotion and F) body movement emotion vs vocal emotion. All correlations are statistically significant ($p = 0.001$).

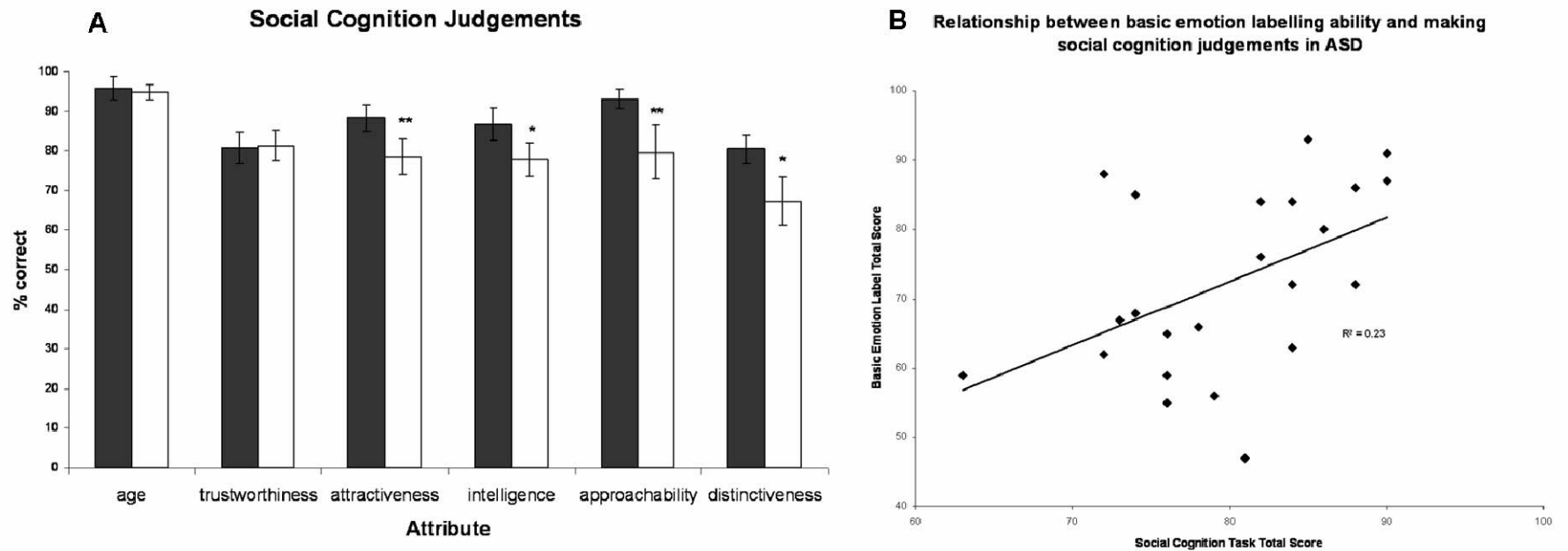


Figure 2A - Percentage of responses in agreement with standardised scores for each attribute in the task of social cognition. Control group mean is in black, ASD group mean is in white. 95% confidence intervals are displayed. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$. B) Correlation between basic emotion labelling ability and performance in tasks of social cognition in the ASD group, ($p = 0.021$).

**Appendix 3 - Cross-modal emotion deficits in adults
with ASD**

**Presented at the 7th annual International Meeting For
Autism Research, London, 2008.**

Generalised emotion recognition deficits in adults with Autistic Spectrum Disorder

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Background

The debilitating social dysfunction integral to autism has been shown to relate to deficits in processing emotional information from human stimuli¹. The majority of investigations into emotion processing in autism have used static images of emotional faces. There is increasing evidence to suggest those with autism may also display deficits in other stimulus domains and sensory modalities^{2,3}.

Objective: We sought to investigate basic emotion recognition across a range of stimulus types and across sensory modalities within the same group of people with ASD, using tasks of comparable format.

Table 1	ASD group	Control group
age	32.5 (10.8)	32.4 (11.1)
gender	16M 7F	17M 6F
Full Scale IQ score	101.5 (18.5)	111.2 (8.5)
Autism Quotient score	34.4 (7.7)	13.1 (5.6)

Figure 1 - Example stimuli from the face emotion label task and a static image from the body movement and voice tasks. Both represent 'anger'.

Methods

23 ASD participants who had previously received a clinical diagnosis of Asperger's Syndrome/High Functioning Autism were recruited in addition to 23 age and gender matched controls (table 1). Participants completed three emotion label tasks using three stimulus types: faces⁴, body movements⁵ and voices⁶. Example stimuli are in figure 1. Participants selected a test label from a choice of five to describe the emotion expressed in the stimulus. Ten trials of happiness, sadness, anger, fear and disgust were presented in random order in the body movement and voice tasks. Seven trials of each emotion were used in the faces task. A t-test was used to assess differences in group performance for each task. ANCOVAs were employed to further investigate the effect of emotion and also the effect of IQ on task performance. Post-hoc tests were then applied to compare group performance for each emotion in each task. Pearson's correlation was used to investigate relationships between task performance in the ASD group.



Table 2	ASD (% accuracy)	Control (% accuracy)	t-value	p-value
Faces task	80	92	3.08	0.003
Body movement task	71	88	4.17	<0.001
Voice task	61	79	5.05	<0.001

Results

The ASD group was significantly impaired in labelling emotion in each of the tasks. See table 2. This was observed across a range of emotions in each task (figure 2) and was not accounted for by differences in IQ score between groups. Within the ASD group, performance in each stimulus type was significantly correlated (figure 3).

Conclusions

Results are indicative of a cross-modal emotion processing deficit in autism. The data demonstrates an emotion deficit which crosses a range of basic emotions, stimulus types and sensory modalities. This implicates a neurobiological substrate that is part of an extended network of emotion processing, rather than structure specific to face processing.

The authors would like to thank all the participants for their involvement in the study and the help and support of Number 8, Autism Initiatives, Edinburgh.

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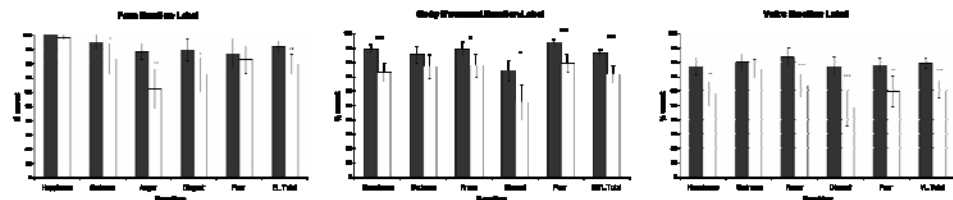


Figure 2 - Percentage of correct responses for each emotion in each emotion label task. Control group mean is in black, ASD group mean is in white. 95% confidence intervals are displayed. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

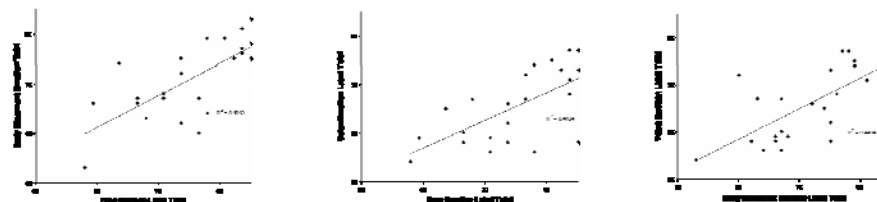


Figure 3 - Correlations between performance in each of the emotion label tasks in the ASD group. All correlations are statistically significant ($p < 0.001$).



**Appendix 4 - Lack of emotion modulation of brain
activation during face processing in ASD**

**Presented at the 8th annual International Meeting For
Autism Research, Chigaco, 2009.**

Lack of emotion modulation of brain activation during face processing in ASD



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Background

When investigating the neural substrate of the social deficits in ASD, many studies have looked at brain activity in response to face stimuli. Whilst many of these often include both emotional and neutral stimuli, it is often unclear whether aberrant brain activation in the ASD group is attributable to deficits in face processing, emotion processing or both. We sought to isolate emotion processing and investigate its neural underpinnings in both control individuals and those with ASD.

Methods

Participants: The ASD group consisted of 12 men with a clinical diagnosis of Asperger Syndrome (8) or autism (4) in accordance with DSM-IV criteria. The ASD group had a mean age of 36.1 years (s.d. 11.8). The control group was matched by age, gender and handedness and consisted of healthy volunteers with no personal or family history of major psychiatric disorders. **Task:** 6 blocks of static Ekman face stimuli were presented, three blocks expressing prototypical fear and three blocks of faces with neutral expressions. Blocks were interspersed with baseline visual fixation. Participants responded by button press to the presentation of each stimulus.

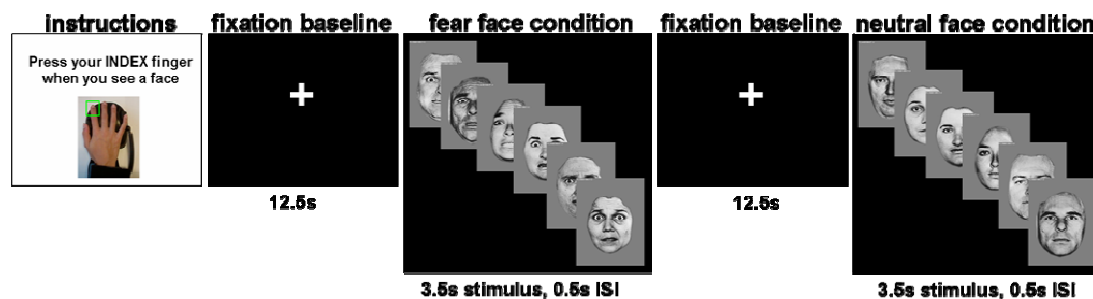


Figure 1 – schematic of functional MRI task design

Scanning: Participants were scanned on a GE 1.5T Signa scanner at the SHEFC Brain Imaging Research Centre, Edinburgh. Functional scans comprised EPI sequence to acquire 99 volumes, TE 40ms, TR 2.5s. Interleaved axial slices were acquired AC-PC aligned with a thickness of 5mm with no gap and matrix size of 64 x 64. Image analysis was conducted in SPM5.

Results

When blocks of fearful faces were contrasted with neutral faces, the control group significantly activated bilateral inferior parietal lobe and also a region of the middle frontal lobe bilaterally. There were no areas of significant activation in the ASD group. A between group contrast revealed a significant difference between groups in both the left and right inferior parietal lobe, ($p=0.004$ and $p=0.01$ corrected).

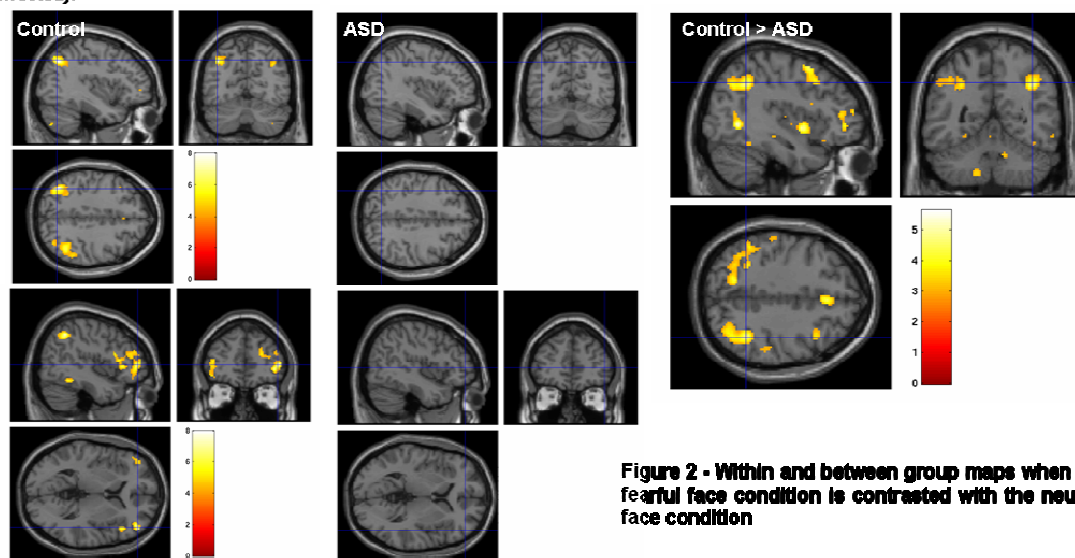


Figure 2 - Within and between group maps when the fearful face condition is contrasted with the neutral face condition

Conclusions

The results indicate that the ASD group fail to respond to the emotional content of face stimuli. This suggests that there is a lack of neural modulation in response to emotion in ASD and this cannot be fully accounted for by a deficit in face processing.